GRAND ENERGY DEVELOPMENT HEALTH CHALLENGES

An Implantable Biomedical Device for Cancer Drug Release and Hyperthermia

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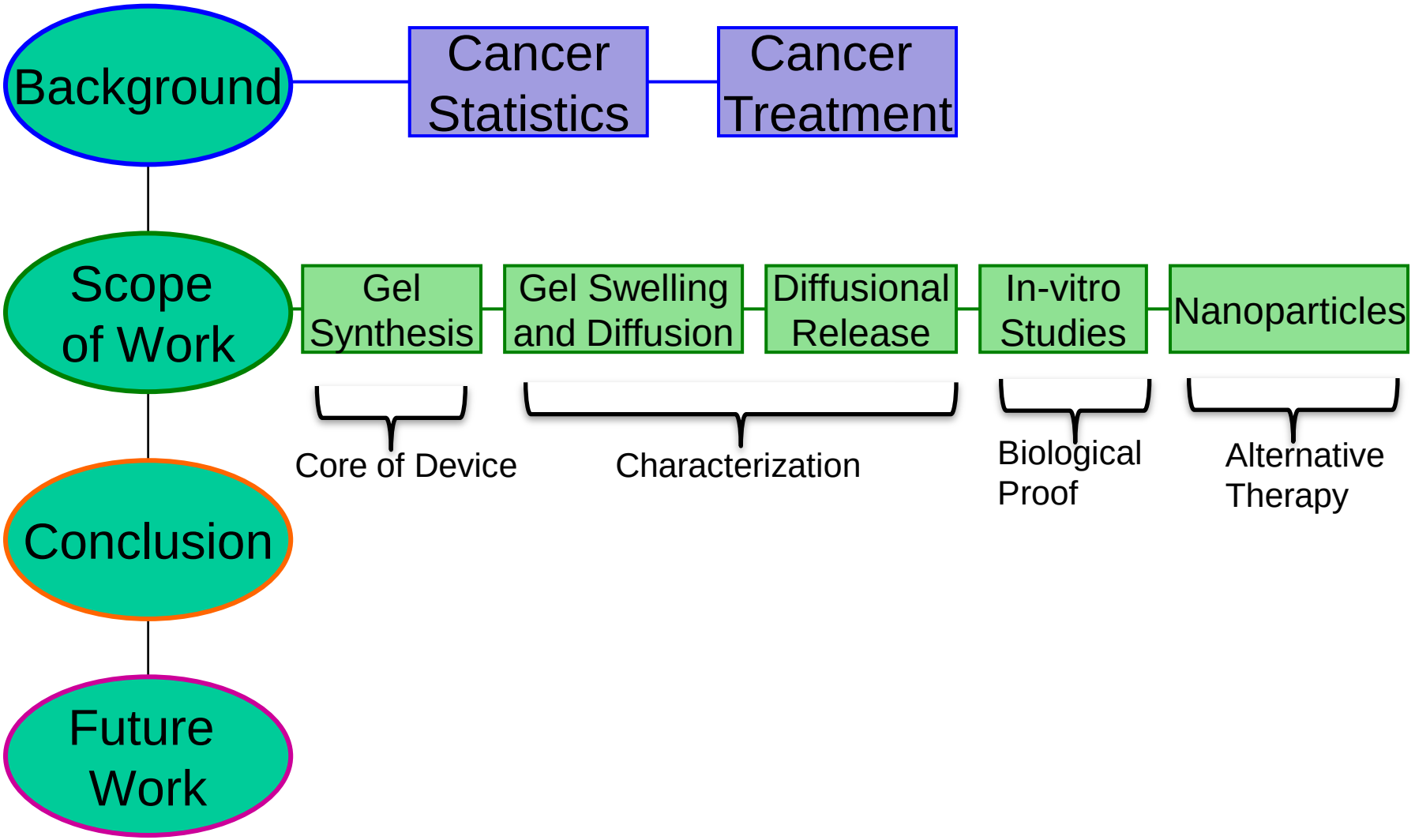
Outline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Cancer Treatment
Scope of Work
Gel Synthesis
Gel Swelling and Diffusion
Diffusional Release
In-vitro Studies
Nanoparticles
Core of Device
Characterization
Biological Proof
Alternative Therapy
Conclusion
Future Work

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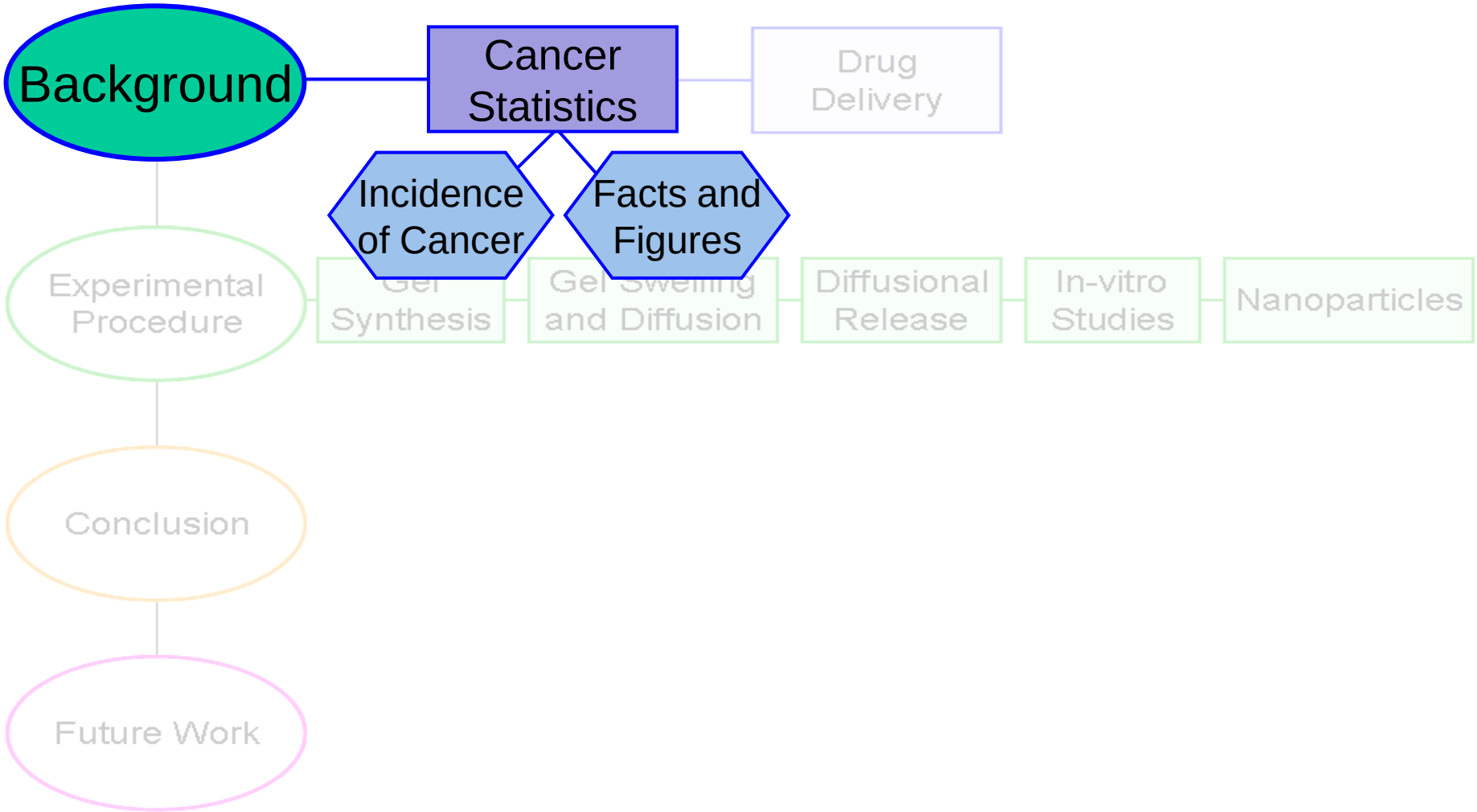
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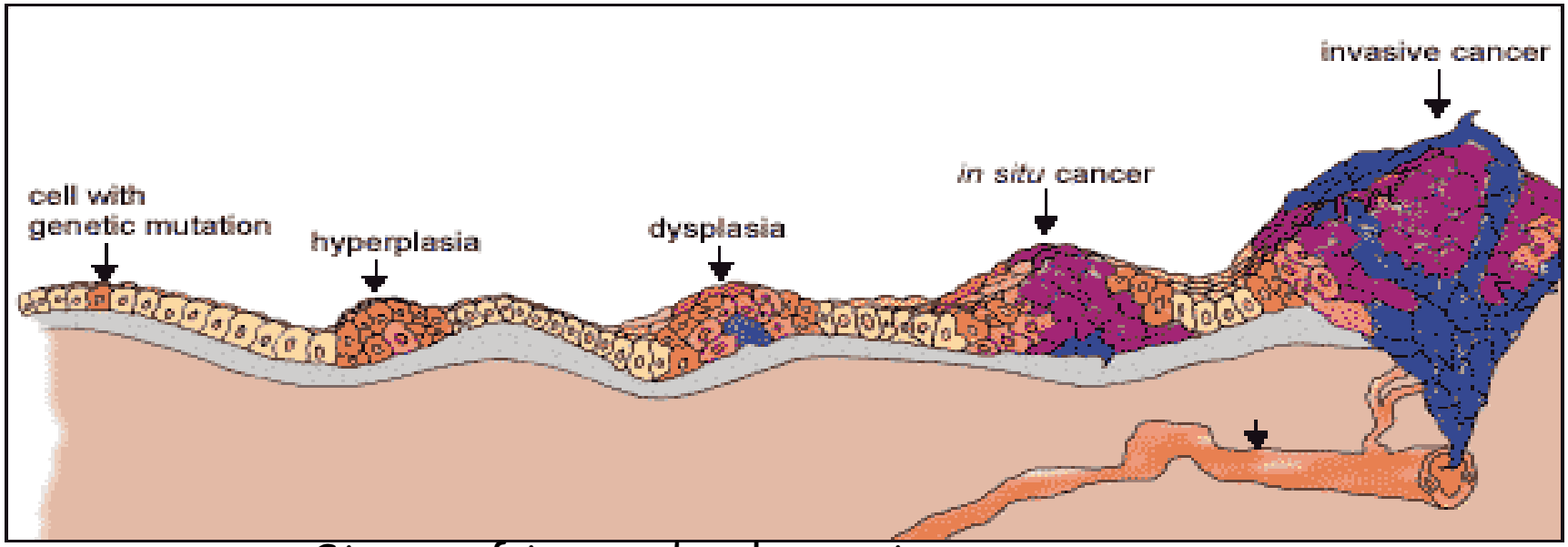
Introduction to Cancer

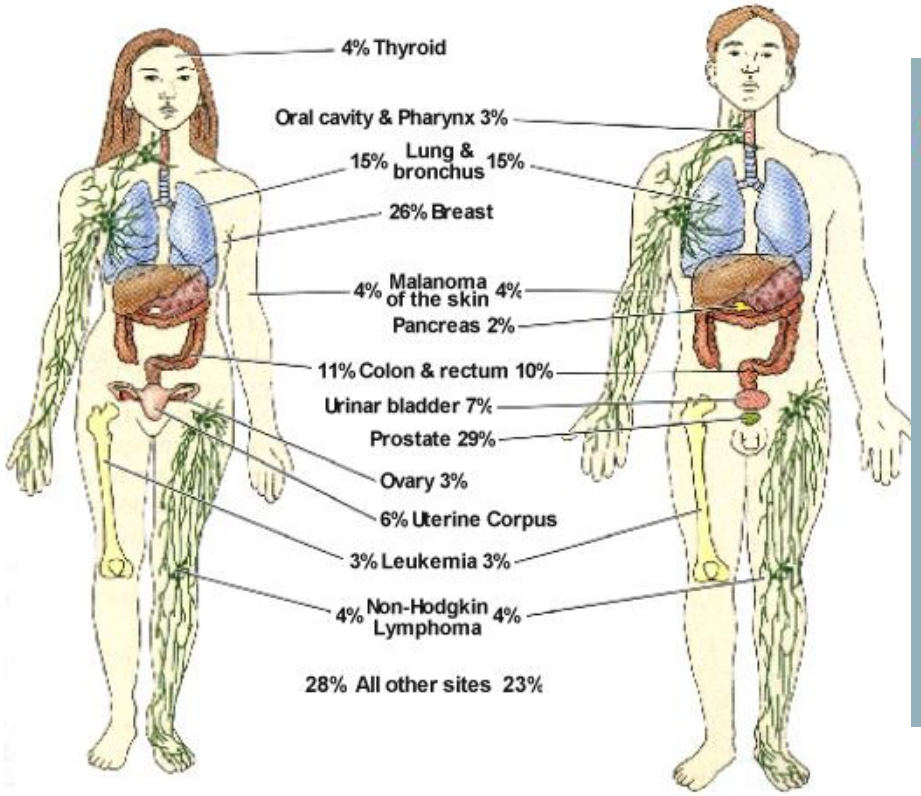
Cancer:

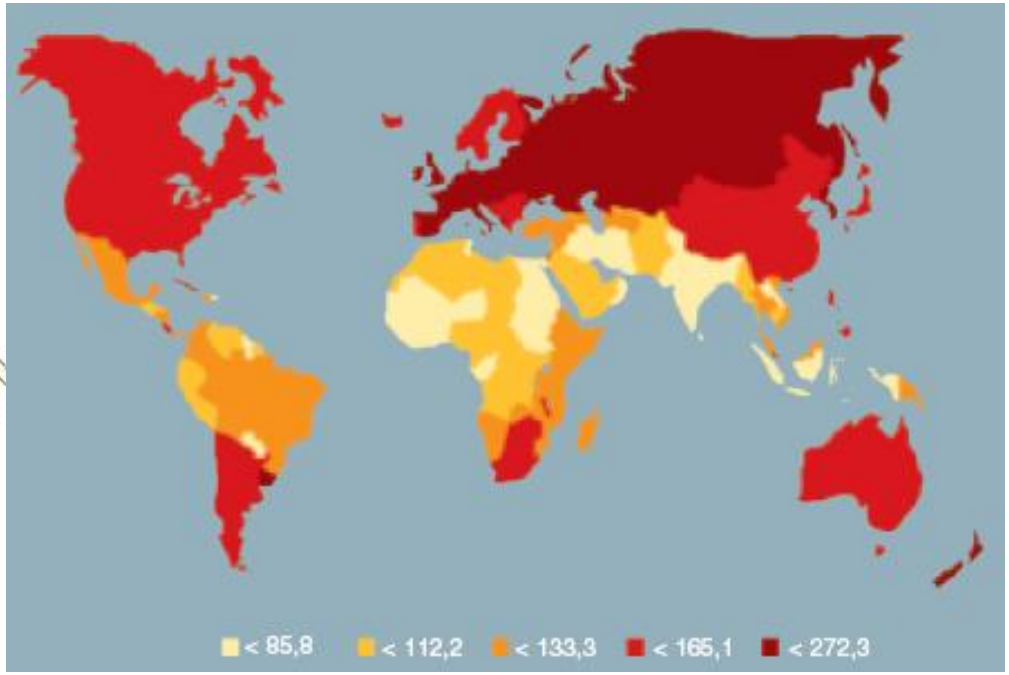
- Group of diseases that cause cells in body to change and grow out of control
- Most types usually form lump or mass called tumor
- Breast cancer begins in breast tissue



Stages of tumor development

Cancer: Facts and Figures World Wide



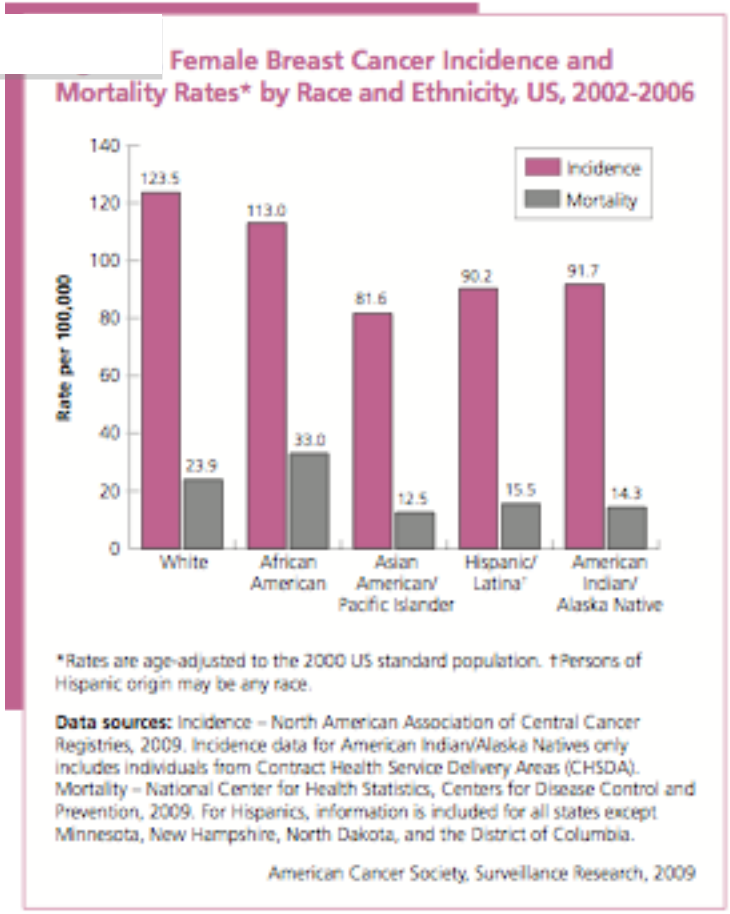


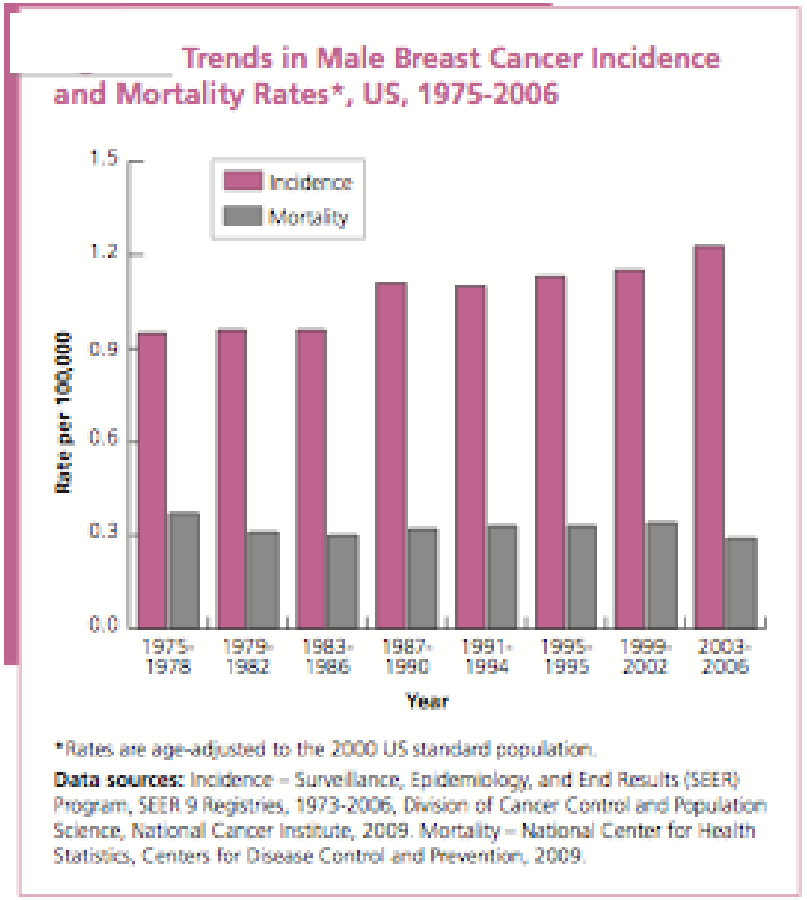
- **10.1 million newly diagnoses/year with ~10% increase**
  - **Second biggest cause of deaths, 2020 possible turning point?**
  - **84 million between 2005-2015**
  - **8 million deaths are attributed to cancer and its complications each year**

American Cancer Society 2007 and Le Cancer Dans le Monde 2004

In the United States…

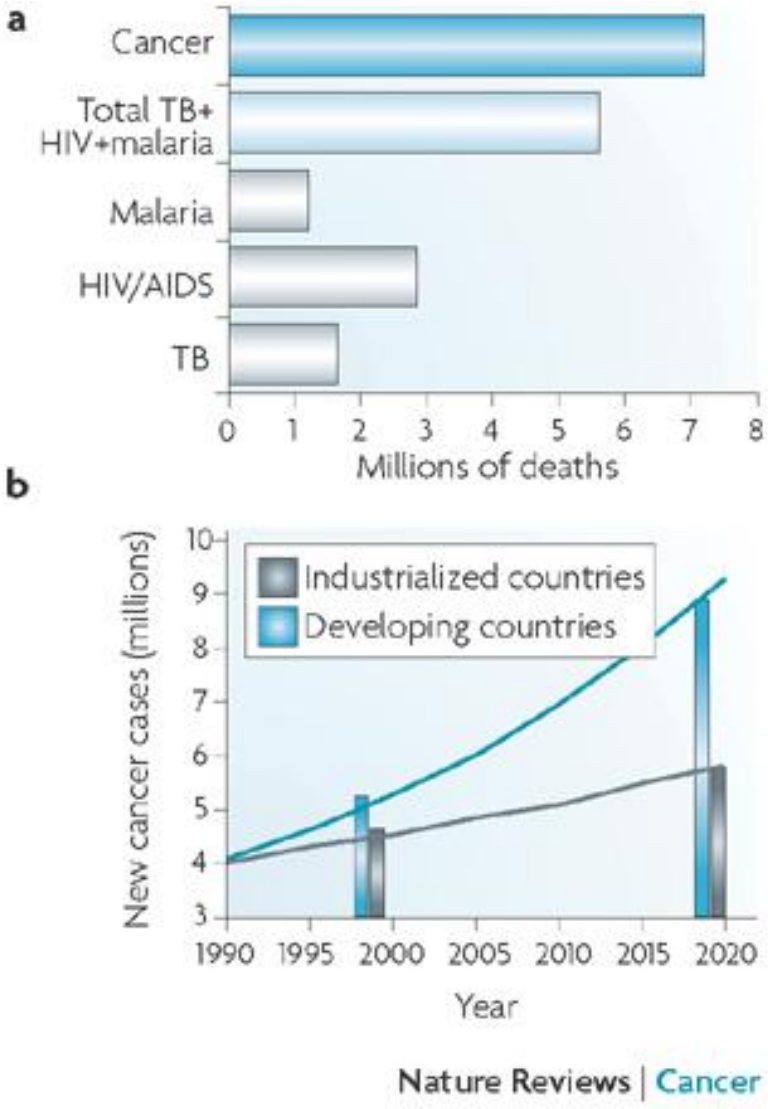
- Half a million deaths from 1.5 million cases
- Breast cancer is not limited to women





Africa on the Spot

- Cancer in Africa is largely overlooked
  - Bigger than HIV/Malaria
- WHO predicts 16 million new cases by 2020
  - 70% from developing countries
  - One-third of cancer preventable, one third treatable if detected early
- Present diagnosis mostly result in death
  - Treatment unaffordable
  - Go home to die



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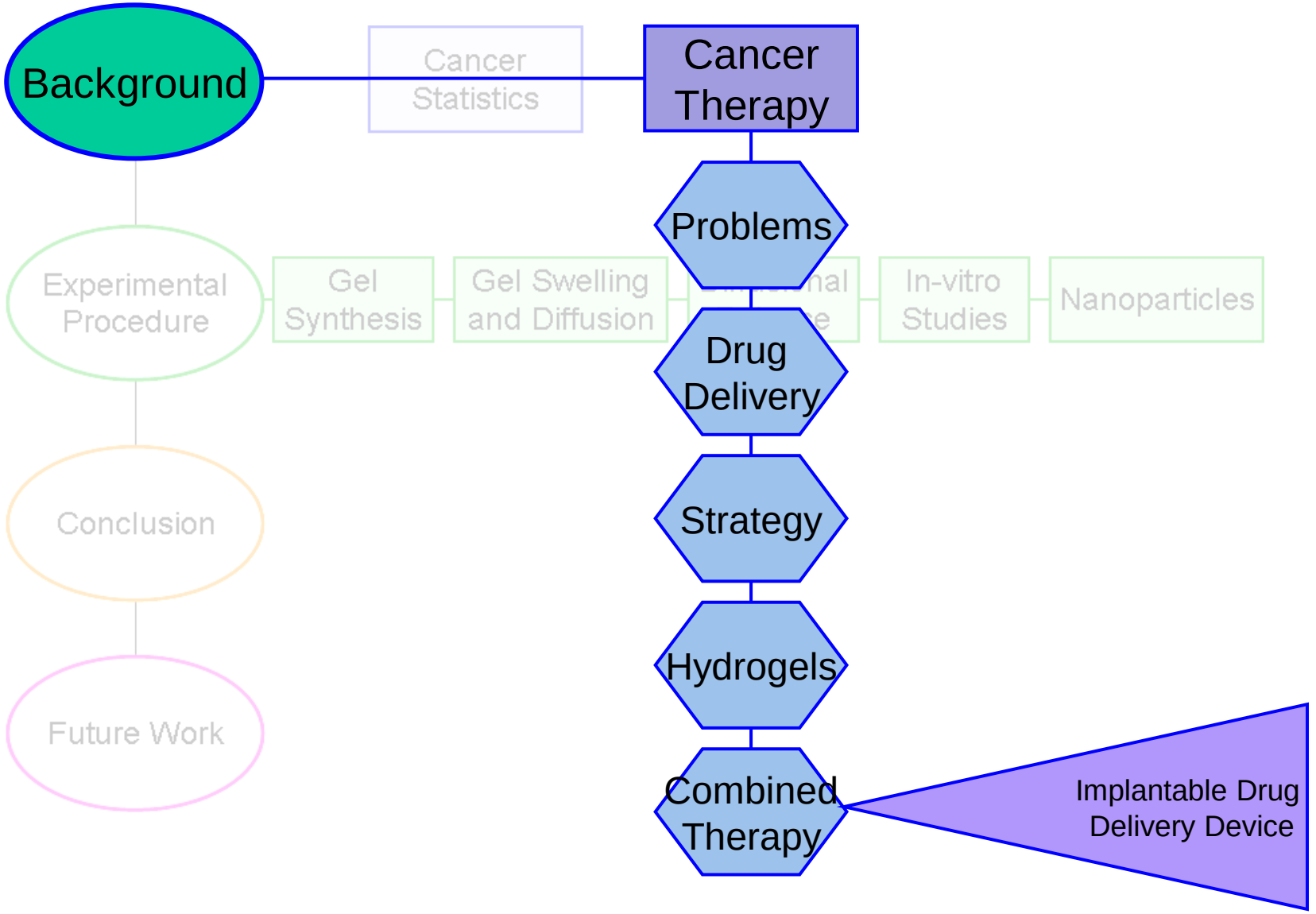
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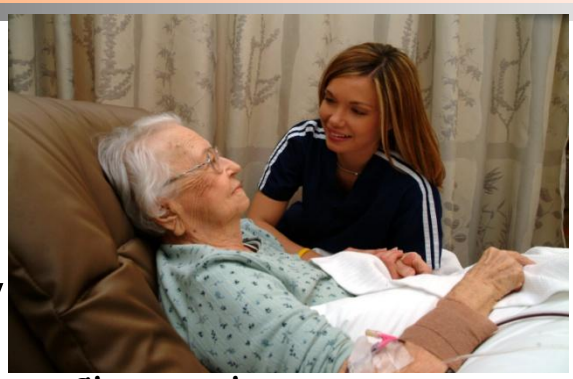
Hydrogels
Combined Therapy
Implantable Drug Delivery Device

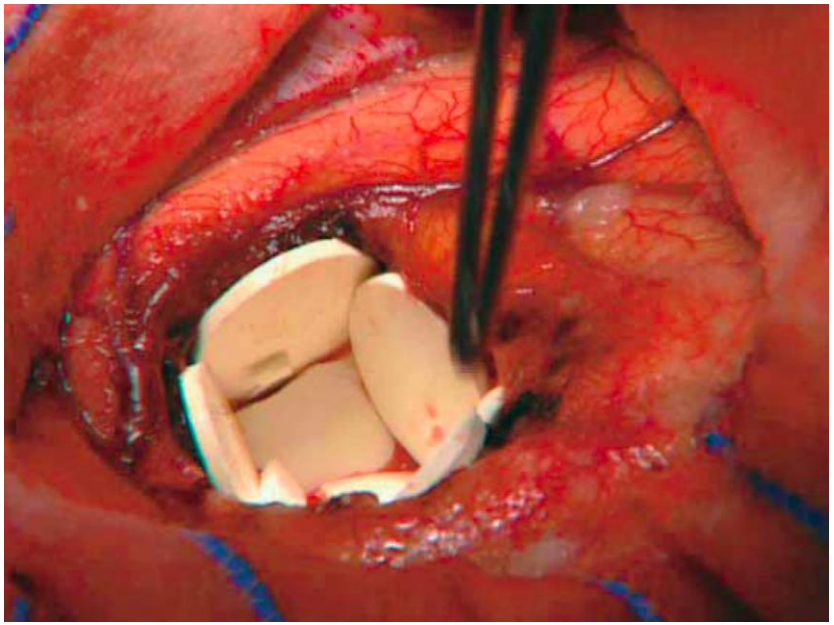
Cancer Therapy

- **Treatments**
  - **Surgery**
  - **Radiation therapy**
    - External
    - Internal
  - **Systemic therapy**
    - Chemotherapy
      - Taxol, Taxotere
    - Hormone therapy
    - Biological therapy



Chemotherapy

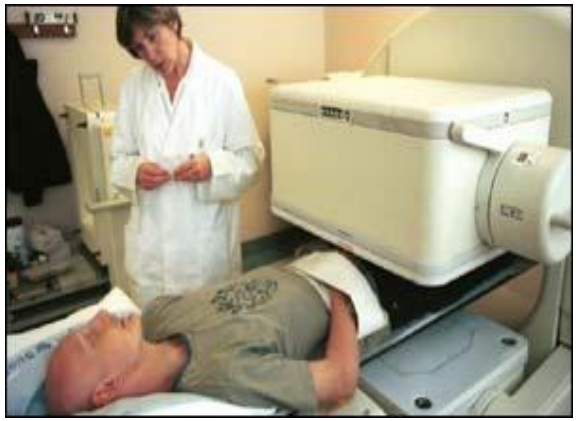
Radiation therapy



Polymer implants loaded with drug after tumor resection (Moses et al. Cancer Cell, 2003)

Problems with Standard Treatments

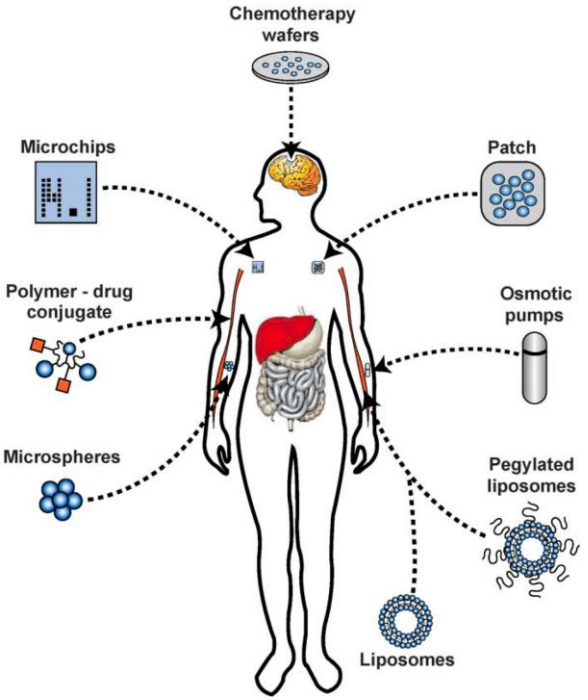
- Possible disease spread post surgery
- Bulk systemic therapy usually not tumor site-specific
  - Low efficacy with less than 1% reaching tumors
  - Side Effects
  - High Concentration



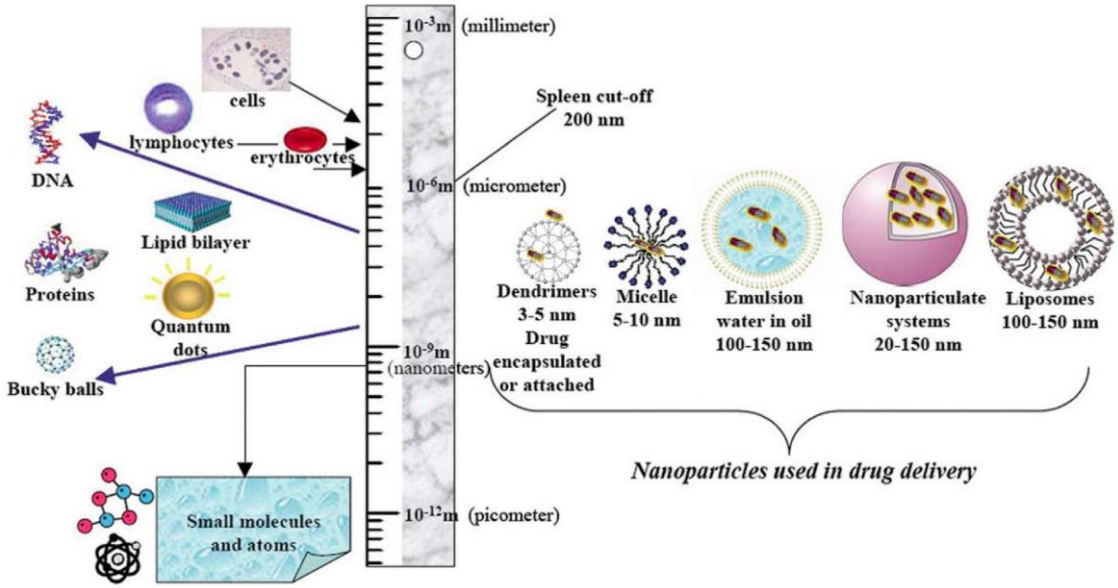
Loss of hair and Fatigue in Chemotherapy

Drug Delivery: A way out

- Different drug delivery strategies exist to mitigate the problems faced with cancer treatment
- Specificity and Controlled delivery still a problem
- Usually requires some chemistry to solve which is sometimes unnecessary especially for solid tumors
- For nanoparticles, limited drug loading and burst effects



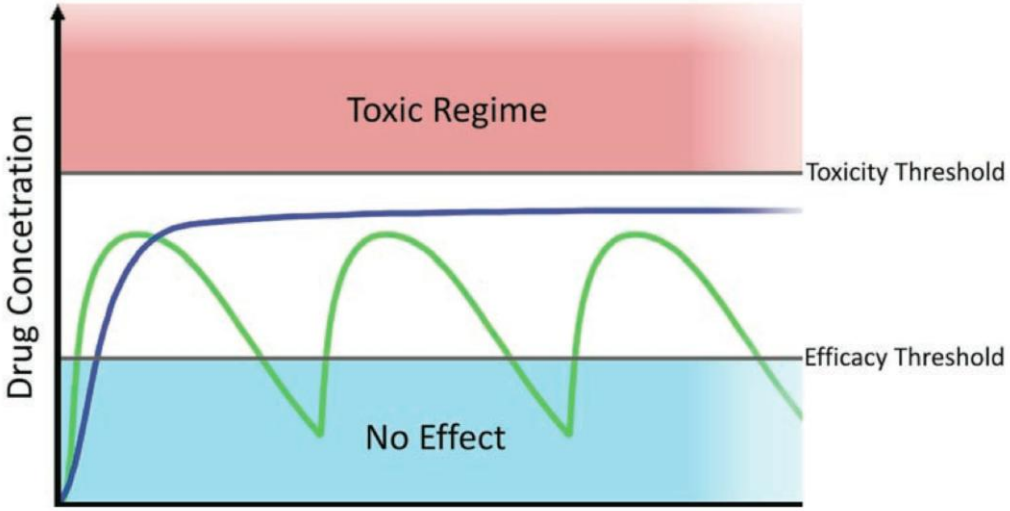
Delivery strategies (Moses et al. Cancer Cell, 2003)



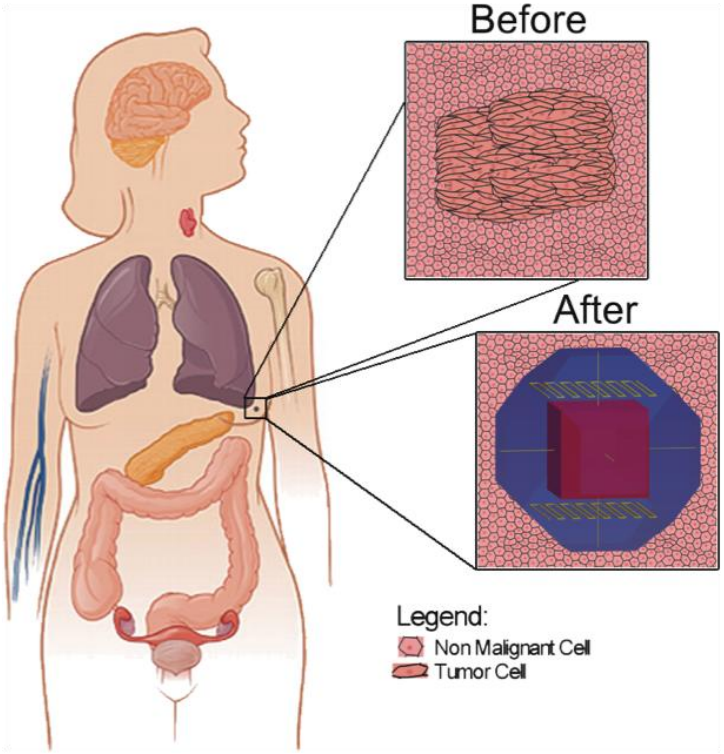
Nanoparticle systems (Arruebo et. al. Nanotoday, 2007)

Strategy: Controlled, Localized Release

- Important for Solid tumors
  - Disease is localized
  - Smaller dose
  - Higher efficacy
  - Reduced side effects



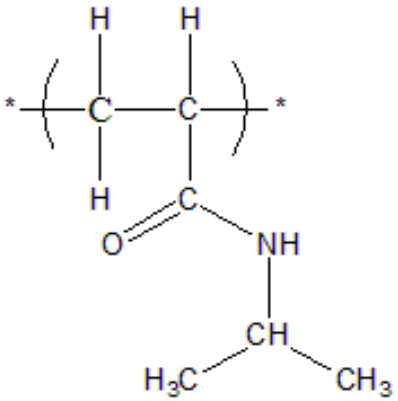
Chemotherapy treatment efficacy



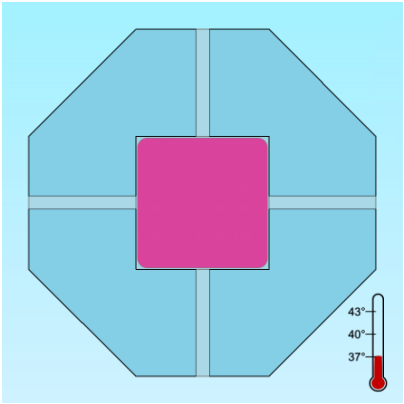
Idea is to design a delivery device for localized therapy

Hydrogels as Drug Carriers

- **Structure**
  - **Polymer network in a liquid medium**
  - **Largely held by hydrogen bonds and van der Waal's forces**
  - **Responds to environmental stimuli**
  - **Shrinking due to hydrophobic collapse**
  - **Poly *N*-Isopropylacrylamide (PNIPA)**

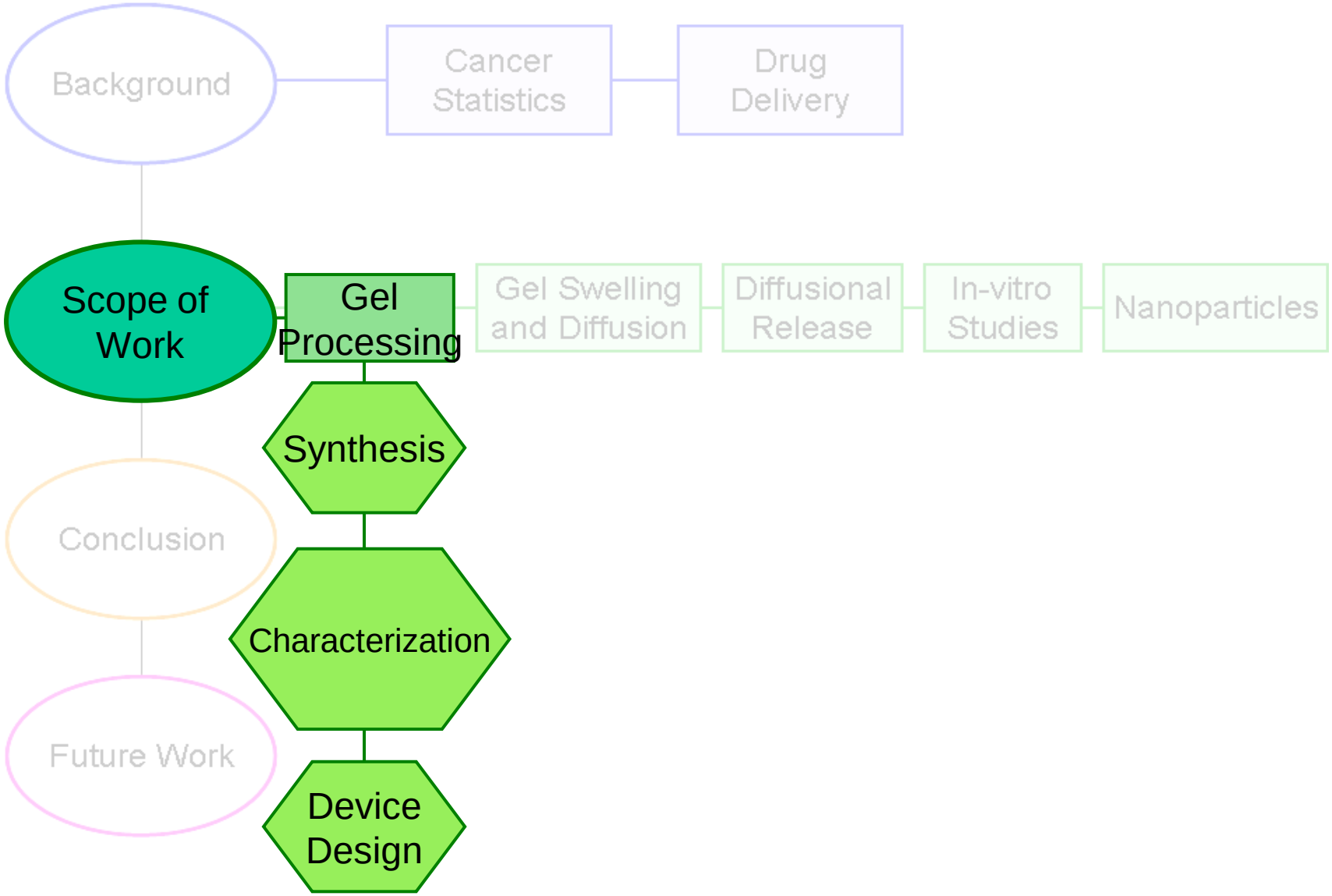


- **Properties**
  - **Unique thermal properties**
    - Phase transition at critical temperature
    - Unique diffusion properties
    - Properties can be controlled by copolymerization



- **Opportunity**
  - **Drug Release**
  - **Residual heat for synergy**

Outline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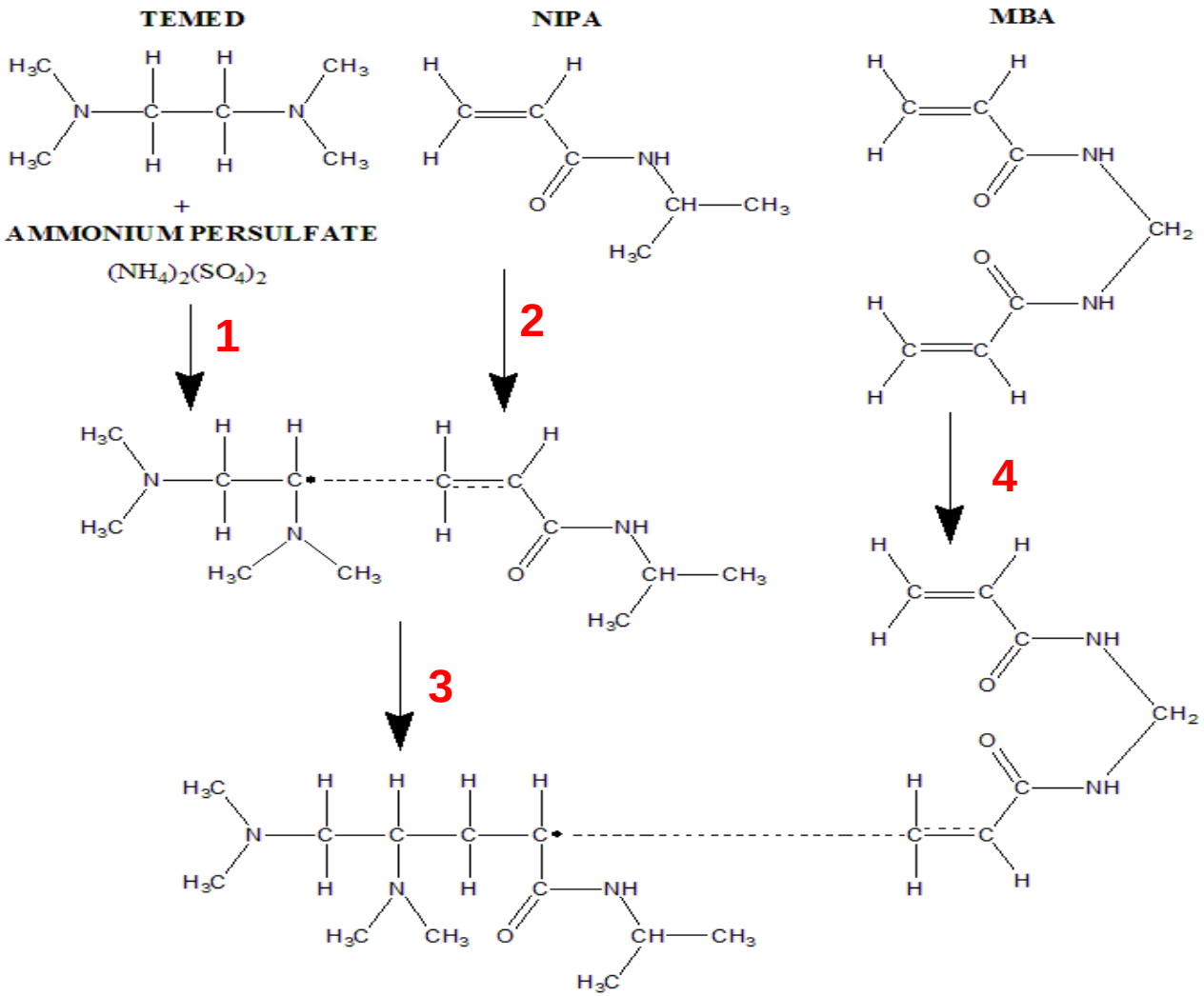
Device Design

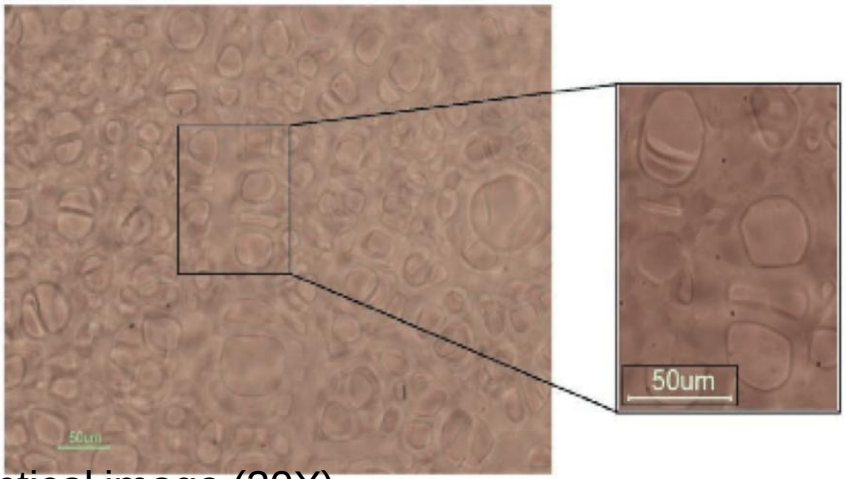
Gel Synthesis



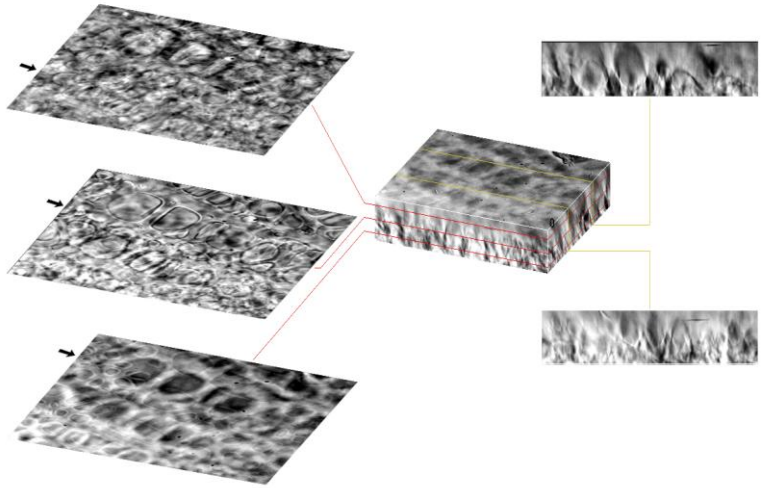
1. Initiation
2. Propagation
3. Polymerization
4. Crosslinking with MBA

Physical Characterization: Microscopy

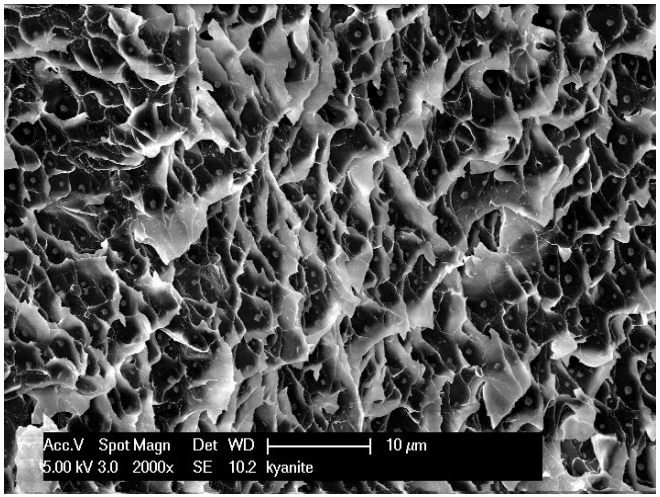
- Microscopy images reveal porous structures

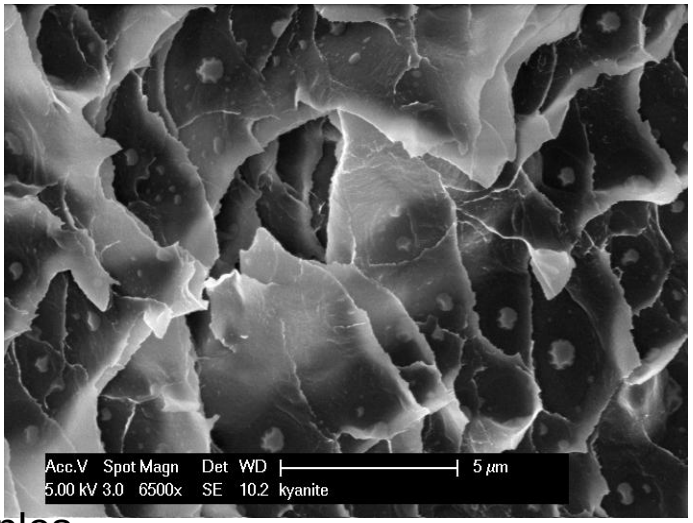


Optical image (20X)



3D Rendering of hydrogel image (20X)

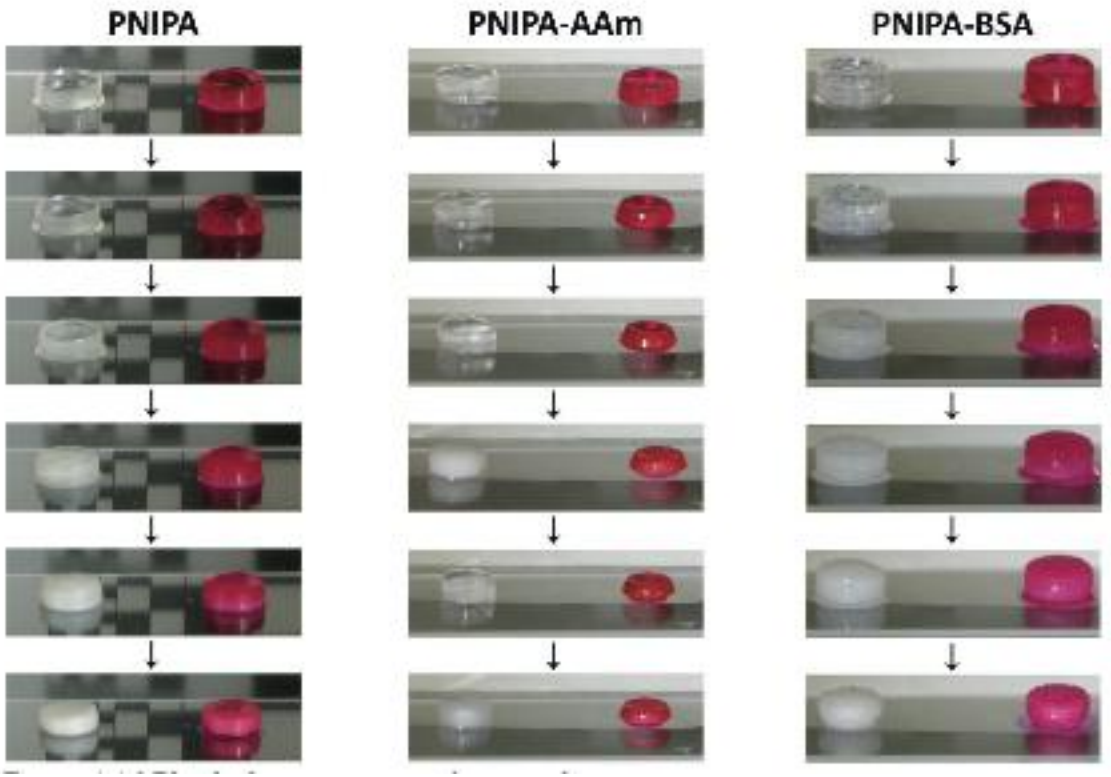




SEM images of dried samples

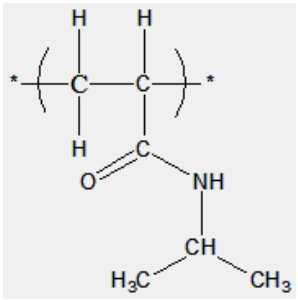
Physical Characterization: Thermal Response

- Hydrogels shrink in the presence of elevated temperatures
- Heat is increased from 25C to 45C
- Gels are observed to turn opaque as they increase above the critical temperature
- Dyed gel is to improve visual clarity
- Dense skin layer observed in hydrophobic copolymer

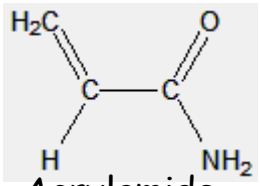


Copolymerization and Phase Transition Temperature

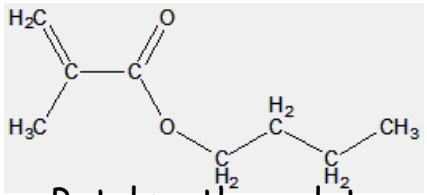
- Transition temperature: 32-34°C
- Addition of co-monomers to control:
  - Phase Transition temperature
  - Degree of expansion and shrinkage
  - Rate of drug release



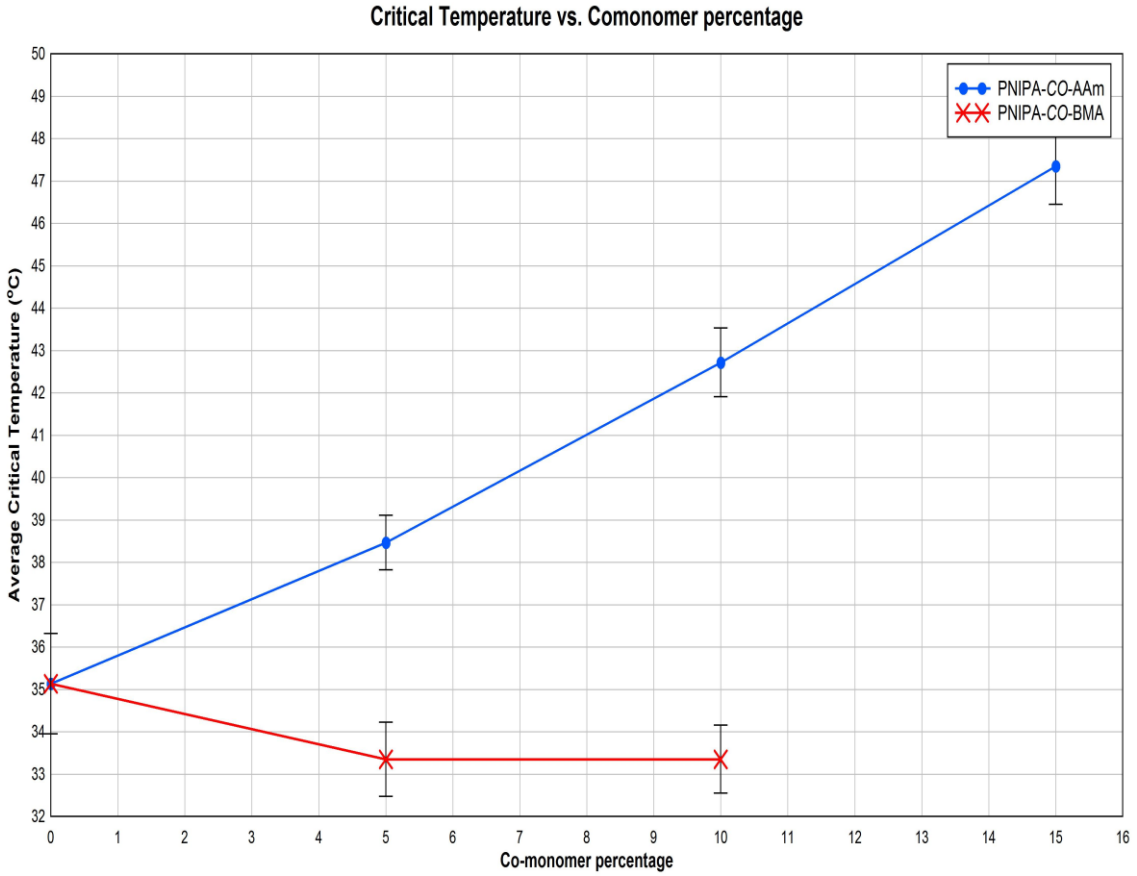
Isopropyl acrylamide



Acrylamide (hydrophilic)

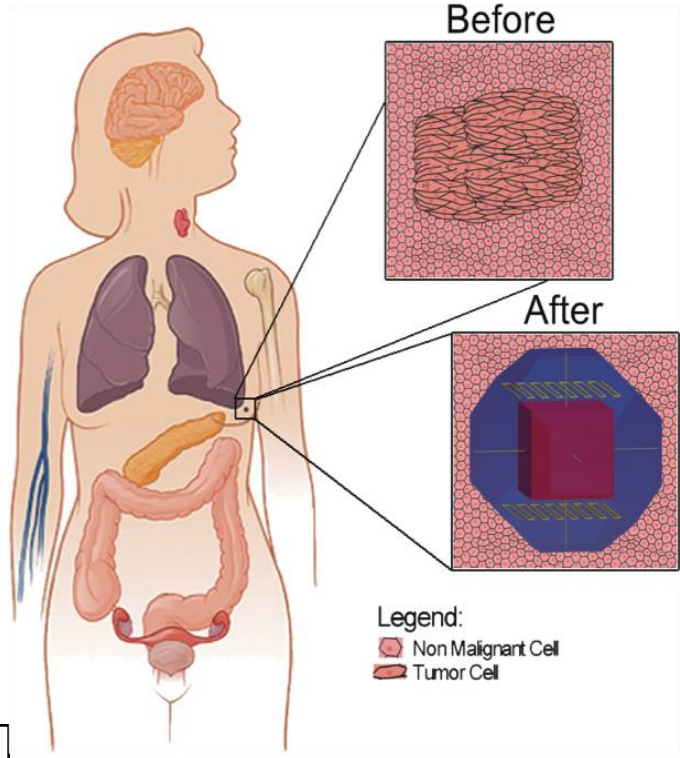


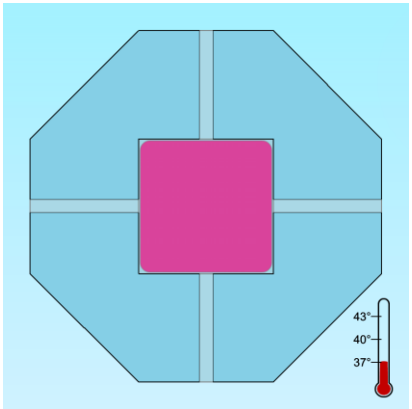
Butyl methacrylate (hydrophobic)

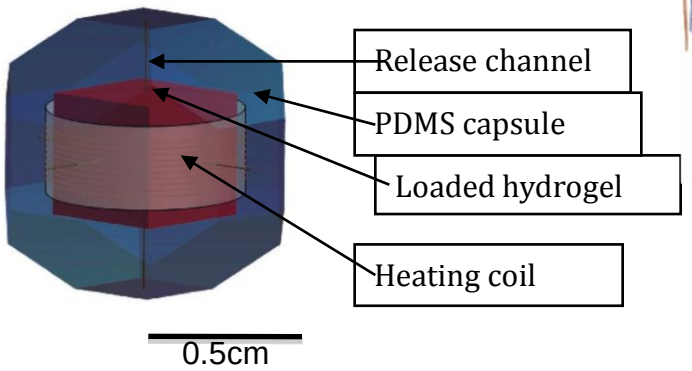


Device Design

- Heat Actuated polymer
- Resistive heating and Hydrogel
- PDMS Encapsulation
- Machined for Tissue Integration
- Micro-channels for release
- Drug Release and Hyperthermia







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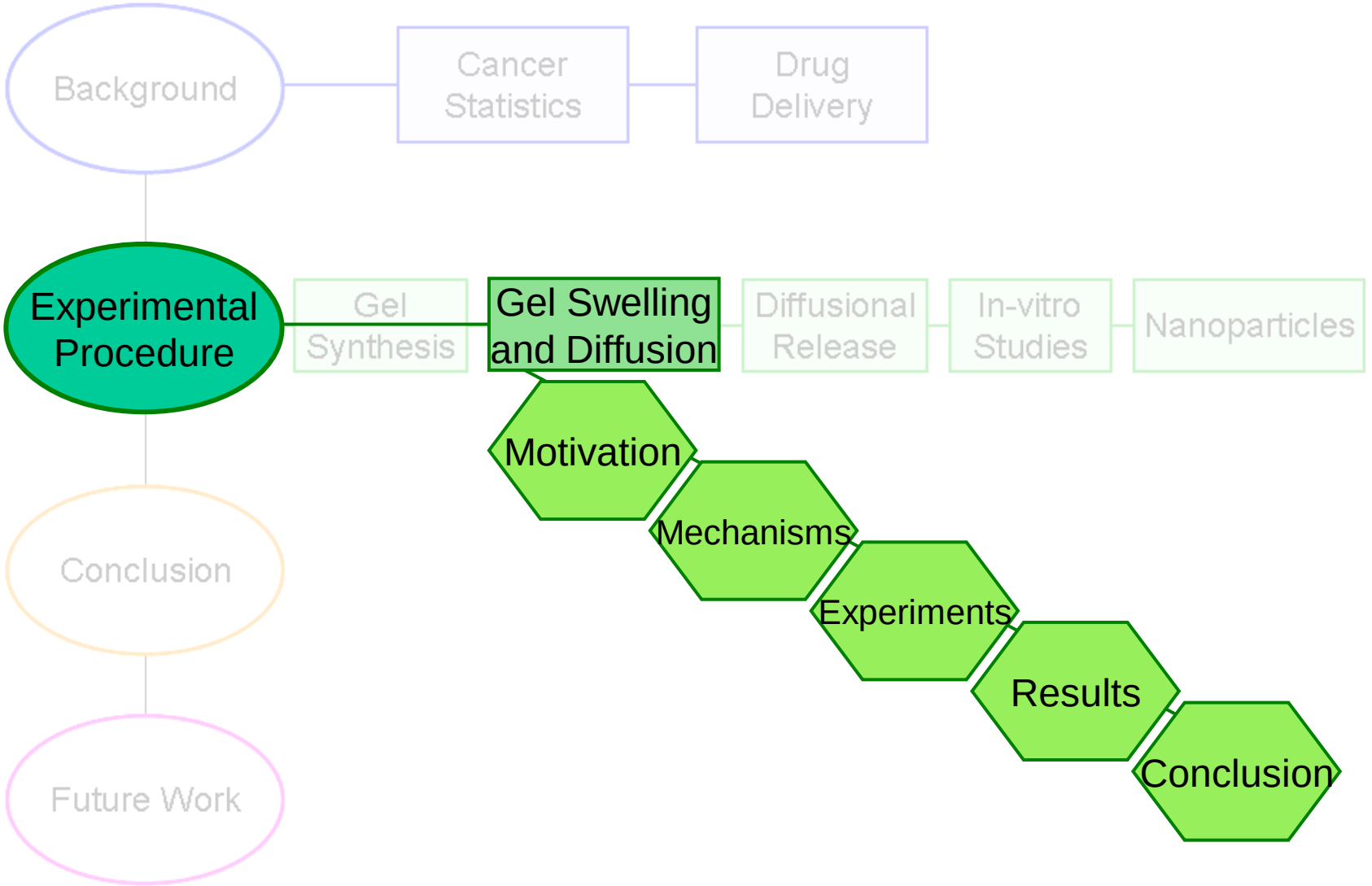
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Experiments
Results
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Motivation

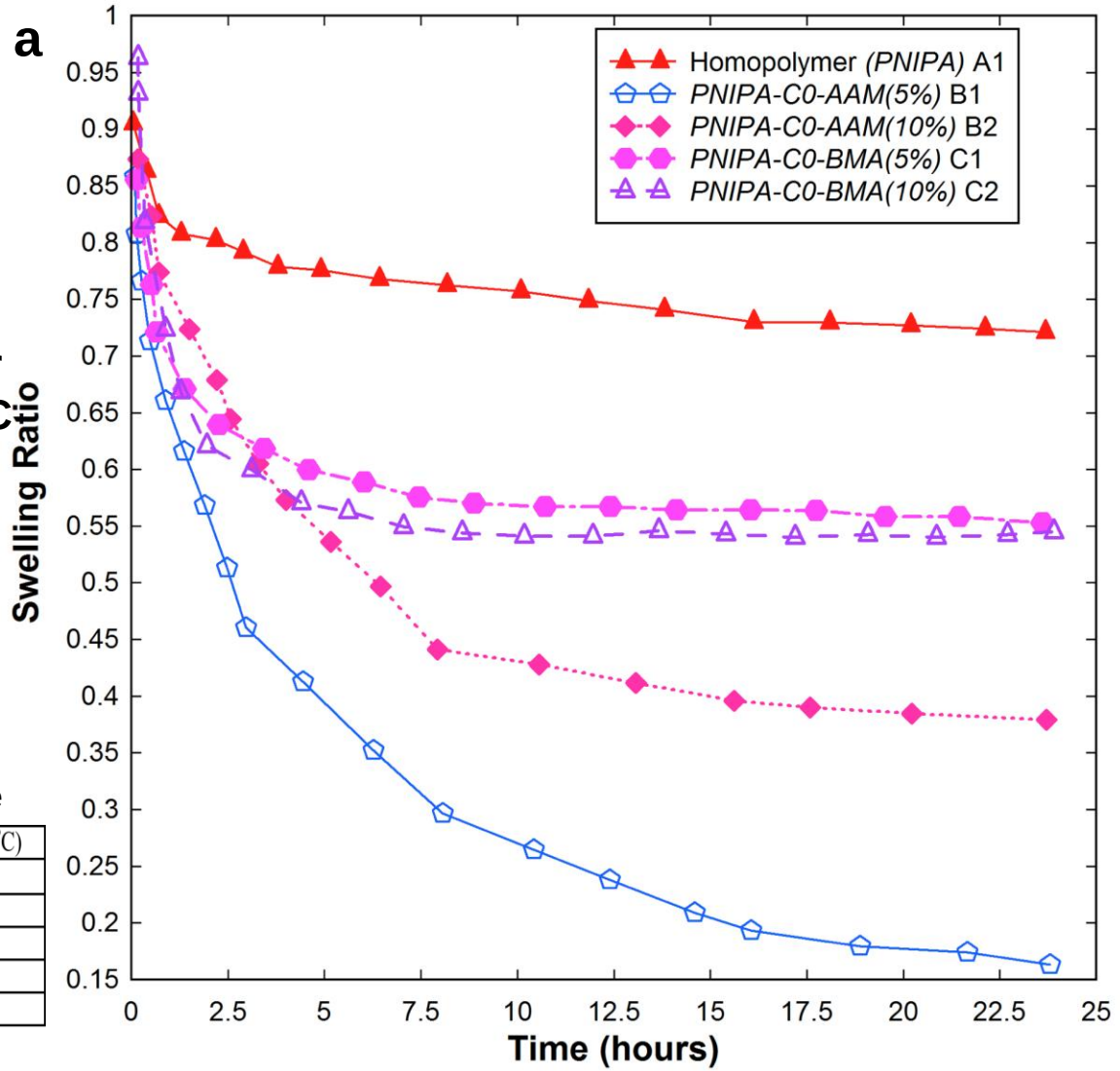
- **Release from gels are usually coupled processes**
  - Mechanical relaxation of polymers
  - Mutual diffusion
  - Hence, diffusion in polymers are mostly non-Fickian
  - Except when diffusion characteristic time is much longer than polymer relaxation time
- **Present study requires use of device within hyperthermic temperature range**
  - No prior studies done within this region
  - Understanding of the swelling processes and transport mechanisms is needed

Swelling Kinetics of Gels

- **Understand gel response in a biomedical environment**
  - **Loaded dried gels in water**
  - **Initial rapid de-swelling**
  - **Predicted by Fourier Series**
  - **Fastest shrinking observed for polymers with LCST below 37C**
  - **Dense skin layer reduces equilibration in hydrophobic copolymers**
  - **Hydrophilic collapse**
    - Slightly unexpected
    - Degree of Crosslinking
    - Higher concentration reduces collapse

Gel Code	Gel Composition	Transition Temperature[1] (°C)
A1	PNIPA (100%)	34.35
B1	PNIPA-co-AAm (95%-5%)	38.20
B2	PNIPA-co-AAm (90%-10%)	42.55
C1	PNIPA-co-BMA (95%-5%)	33.30
C2	PNIPA-co-BMA (90%-10%)	33.45

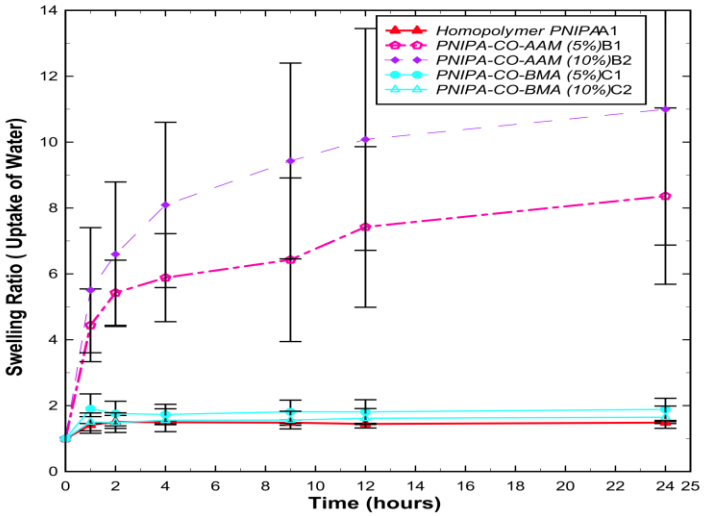
DSC Measurements



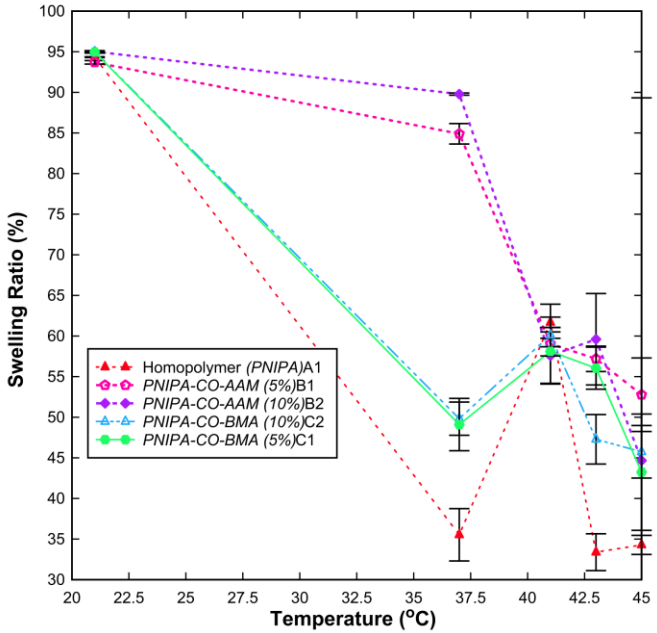
Swelling Ratio at 37C

Equilibrium Swelling

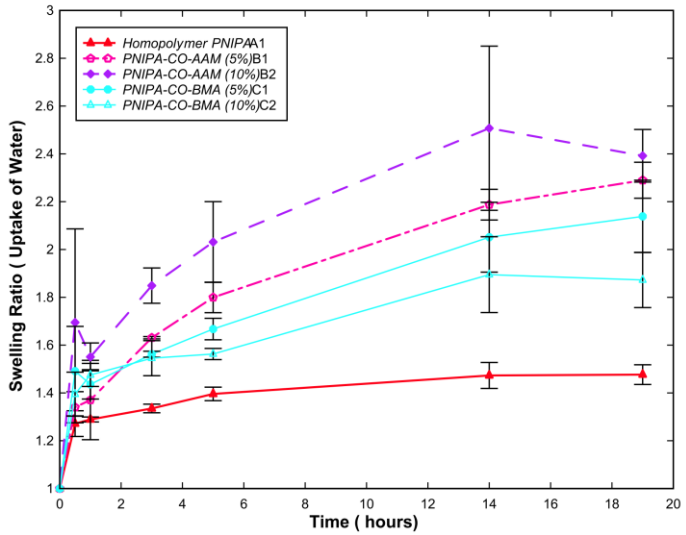
- Higher swelling in hydrophilic variants
  - More hydrogen bonds
- Increasing temperature increases hydrophobic interactic
  - Enhances collapse
  - Drastic reduction between transition



Equilibrium swelling at 37C



Equilibrium swelling ratio between 37C-45C

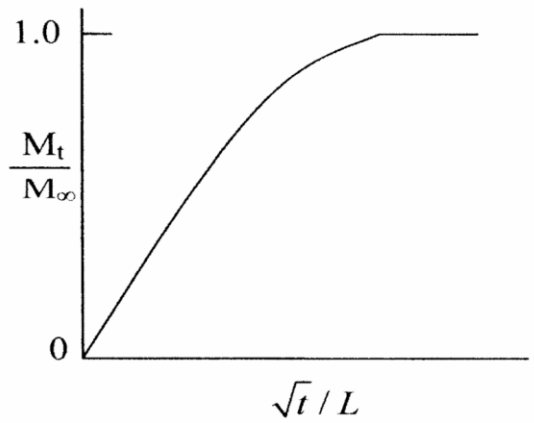


Equilibrium swelling at 43C

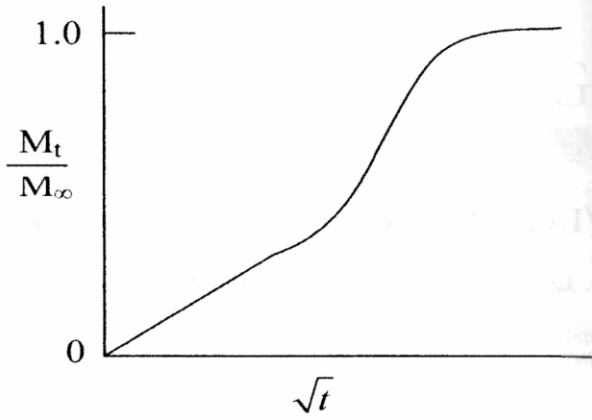
Diffusion Mechanisms

$$\frac{M_t}{M_\infty} = kt^n$$

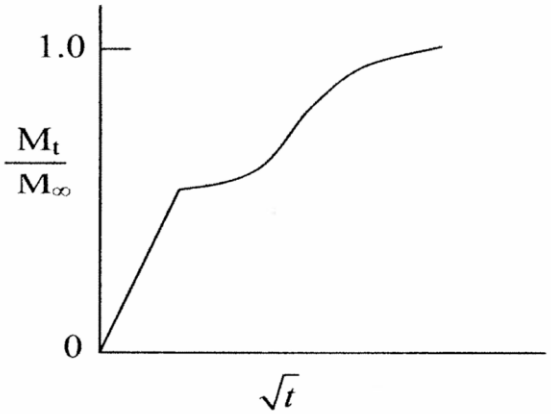
- For Fickian, n=0.5
- Non- Fickian diffusio
  - For case II, n=1
  - Anomalous lie between
  - Due to swelling of polymer



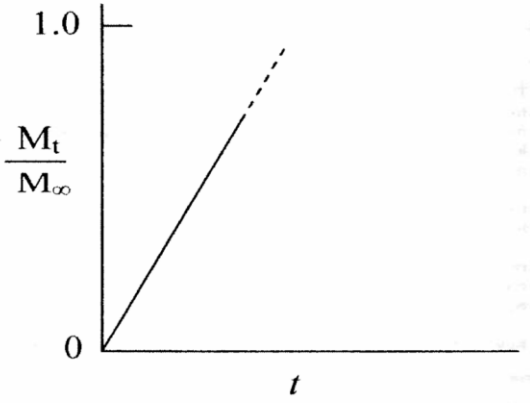
(a) classical



(b) sigmoidal



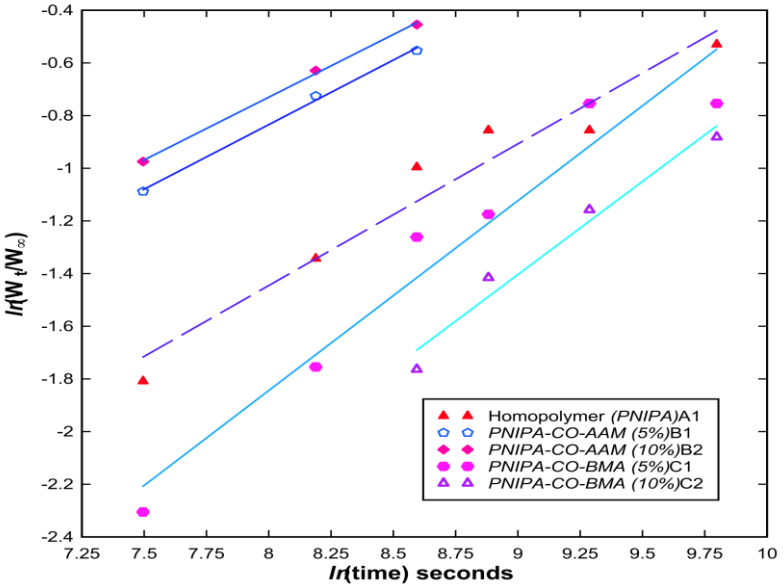
(c) two-step



(d) case II

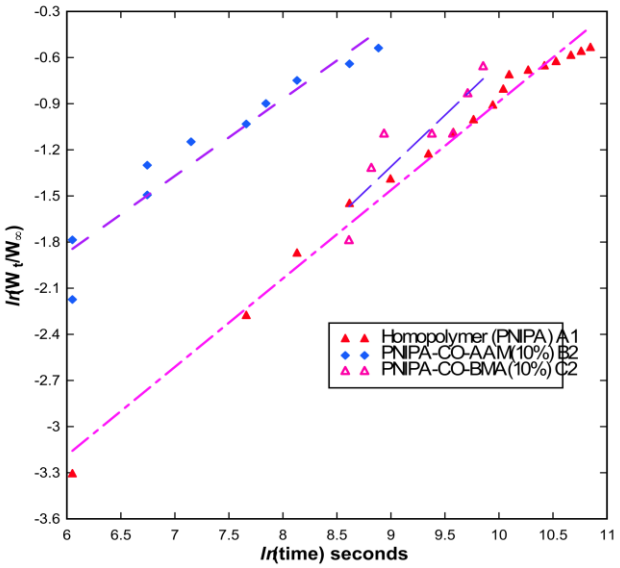
(Kee et al, 2005)

Mechanisms Examined



Rhodamine dye at 37C

$$\ln\left(\frac{M_t}{M_\infty}\right) = n\ln t + \ln k$$



Paclitaxel at 37C

Gel Code/Temperature (°C)	A1 PNIPA	B1 PNIPA-co-AAm (95%-5%)	B2 PNIPA-co-AAm (90%-10%)	C1 PNIPA-co-BMA (95%-5%)	C2 PNIPA-co-BMA (90%-10%)
37	0.54	0.50	0.50	0.72	0.71
41	-	1.88	0.53	0.59	0.71
43	-	3.97	0.63	0.51	0.51
45	-	0.55	0.60	0.77	0.56

Rhodamine dye Fits

Gel Code	A1 PNIPA	B2 PNIPA-co-AAm (90%-10%)	C2 PNIPA-co-BMA (90%-10%)
n	0.56	0.50	0.67
R^2	0.99	0.96	0.90

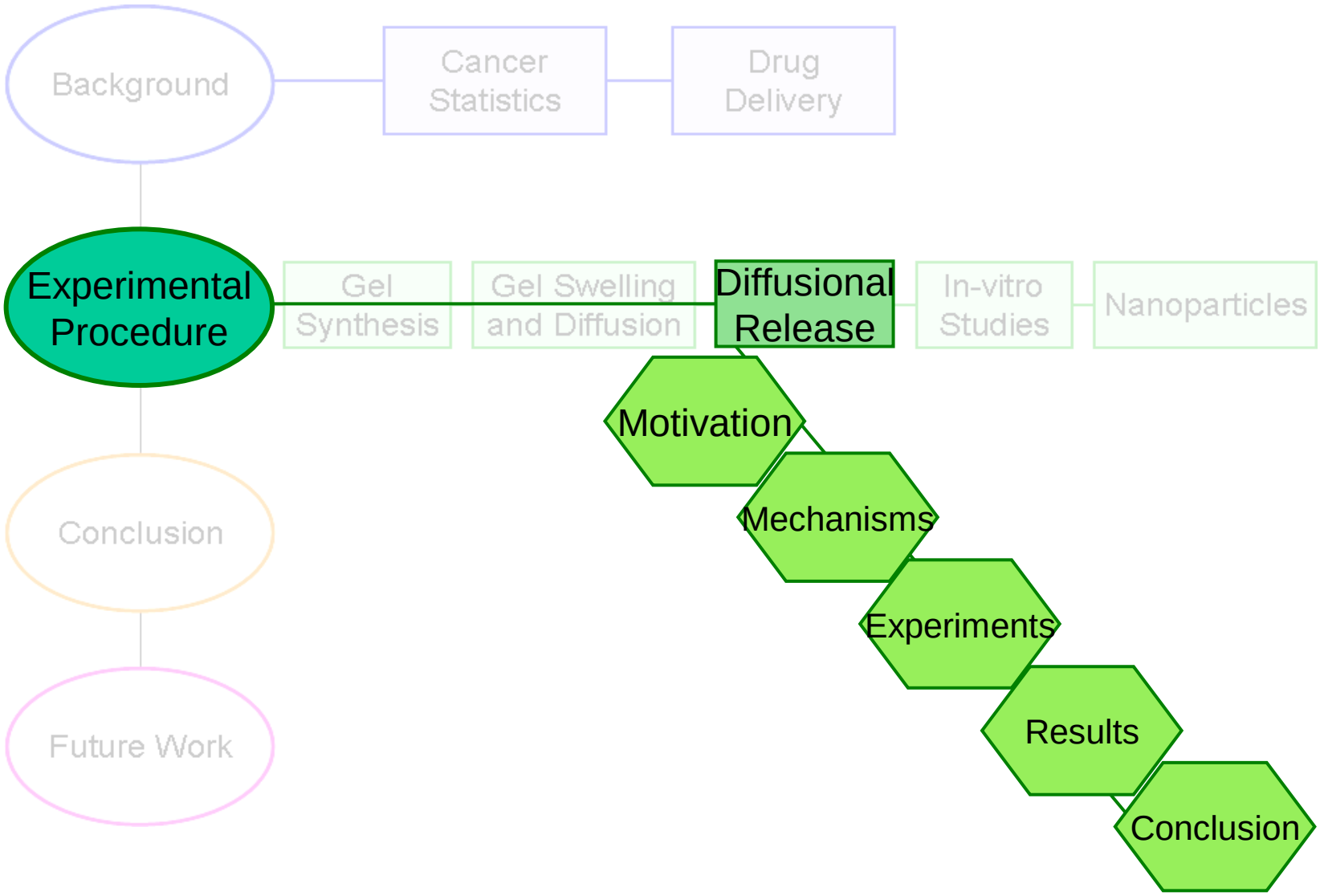
Paclitaxel Fits

- Mechanisms are largely anomalous
- Some Fickian diffusion observed
- Rhodamine and paclitaxel fits agree well
- Supercase transport mechanism: may be extra pumping action associated with transition

Conclusions

- Swelling ratio, loading capacity and drug release rate can be modified by co-polymerization
- Mechanism of transport is mostly non-fickian within hyperthermic range
- Provides information for relevant mechanism towards the design of a delivery device for potential synergy
  - Loading amount of drug
  - Basis for active and passive devices

Outline


Background
Cancer Statistics
Drug Delivery
Experimental Procedure
Gel Synthesis
Gel Swelling and Diffusion
Diffusional Release
In-vitro Studies
Nanoparticles
Motivation
Mechanisms
Experiments
Results
Conclusion
Conclusion
Future Work

Motivation

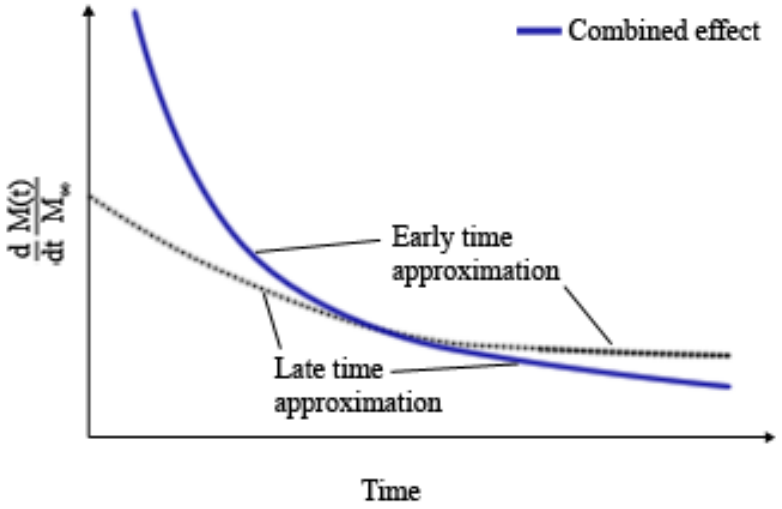
- **Release from gels shown to be non-Fickian**
  - **Diffusion is the predominant mechanism**
  - ***n* values are closer to 0.5 than 1**
- **Diffusion studies needed to predict release rate**
  - **Fundamental effects of hyperthermic temperature on drug release**
  - **Temperature dependence?**
  - **Programming drug release in device depends on good fits**

Diffusion Mechanisms

- **Monolithic Model**

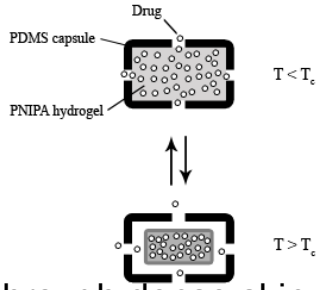
Early time $$\frac{dM(t)}{dt} = 2M_{total}\left[\frac{D}{\pi r^2 t}\right]^{\frac{1}{2}}$$

Late time $$\frac{dM(t)}{dt} = \frac{8DM_{total}}{r^2}\exp\left(-\frac{D\pi^2 t}{r^2}\right)$$

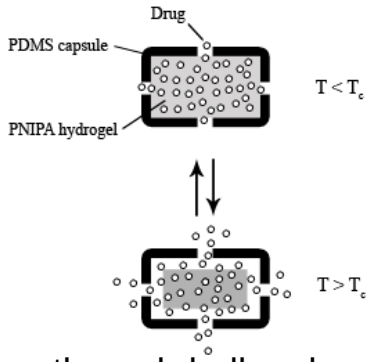


- **Membrane Model**
  - **Dense skin layer controls release rate**

$$\frac{dM(t)}{dt} = \frac{V_m A_g P M_{total}}{V_g^2}\exp\left(\frac{A_g}{V_g}Pt\right)$$



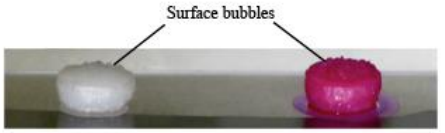
Diffusion through dense skin

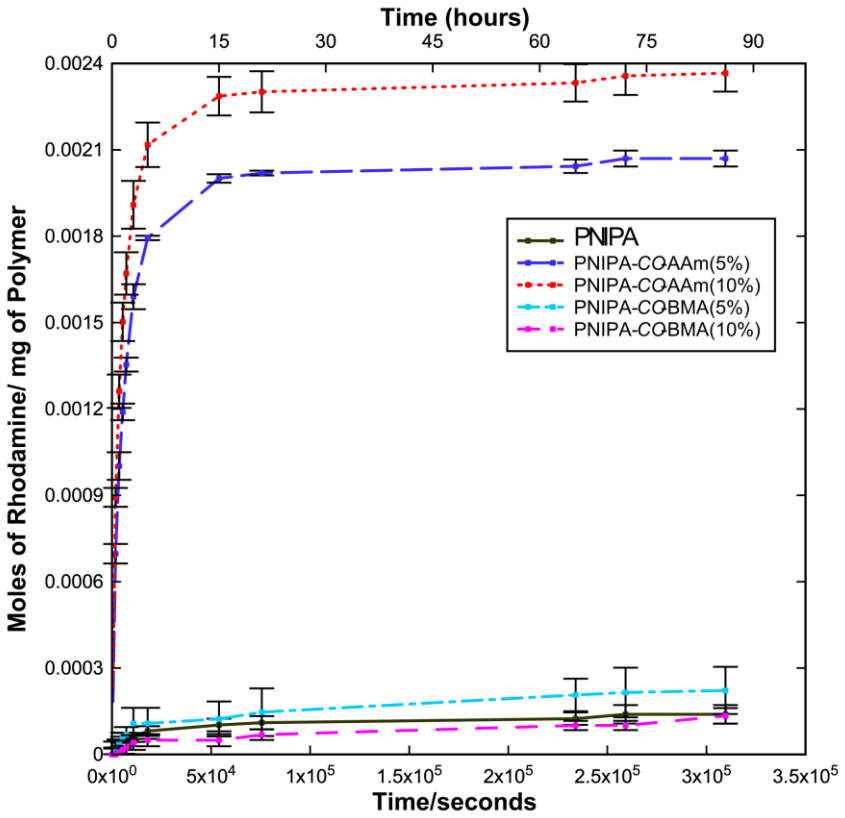


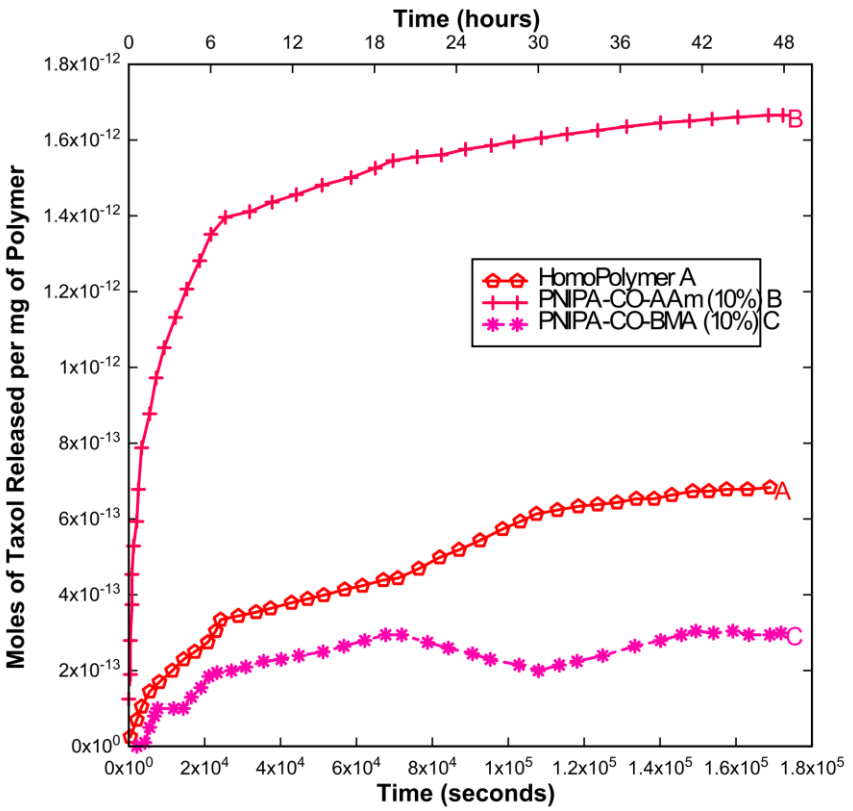
Diffusion through bulk polymer

Release Profiles at 37C

- **Release profiles are similar for rhodamine and paclitaxel**
  - **Each gel has released about 90% of its content**
  - **Hydrophobic release limited by impermeability of surface**



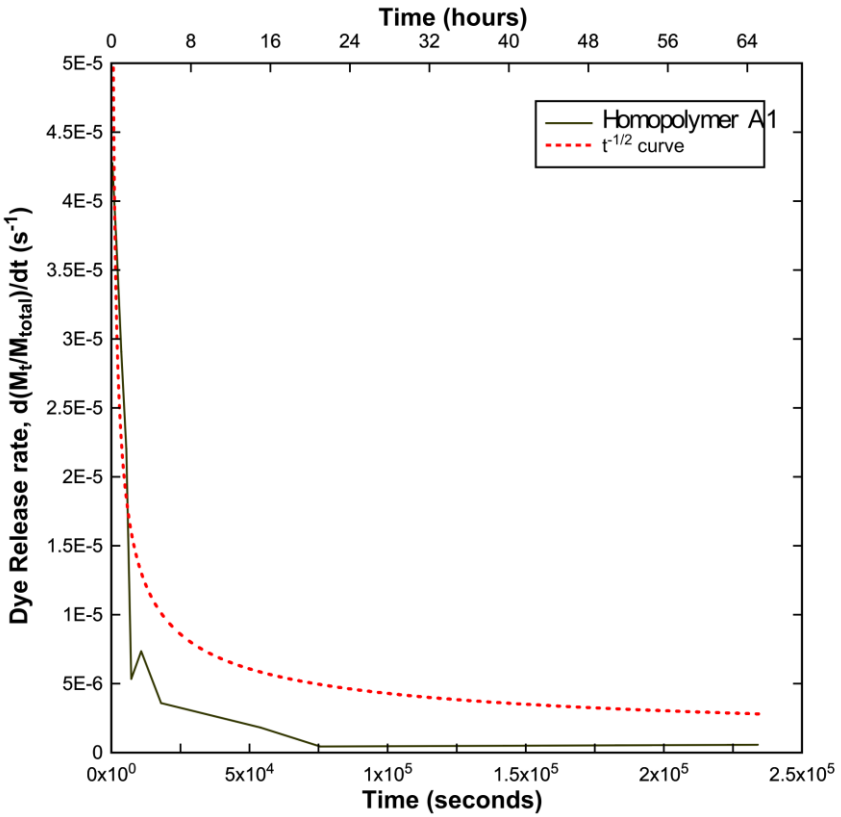




Monolithic: model vs. actual

Homopolymer – slow release

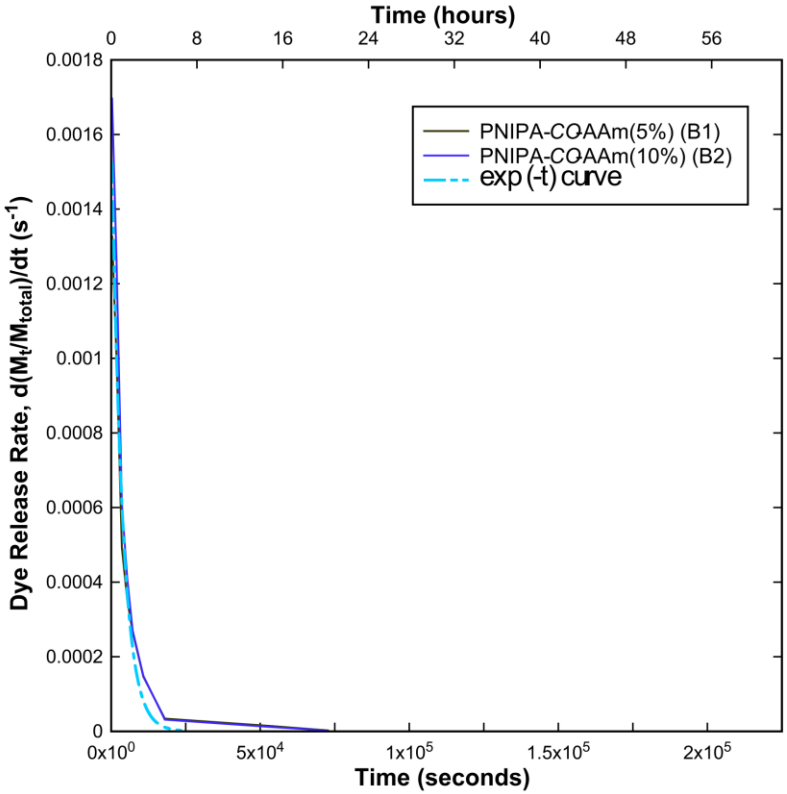
Early time model



$$\frac{dM(t)}{dt} = 2M_{total}\left[\frac{D}{\pi r^2 t}\right]^{\frac{1}{2}}$$

Hydrophilic Copolymer – Fast release

Late time model

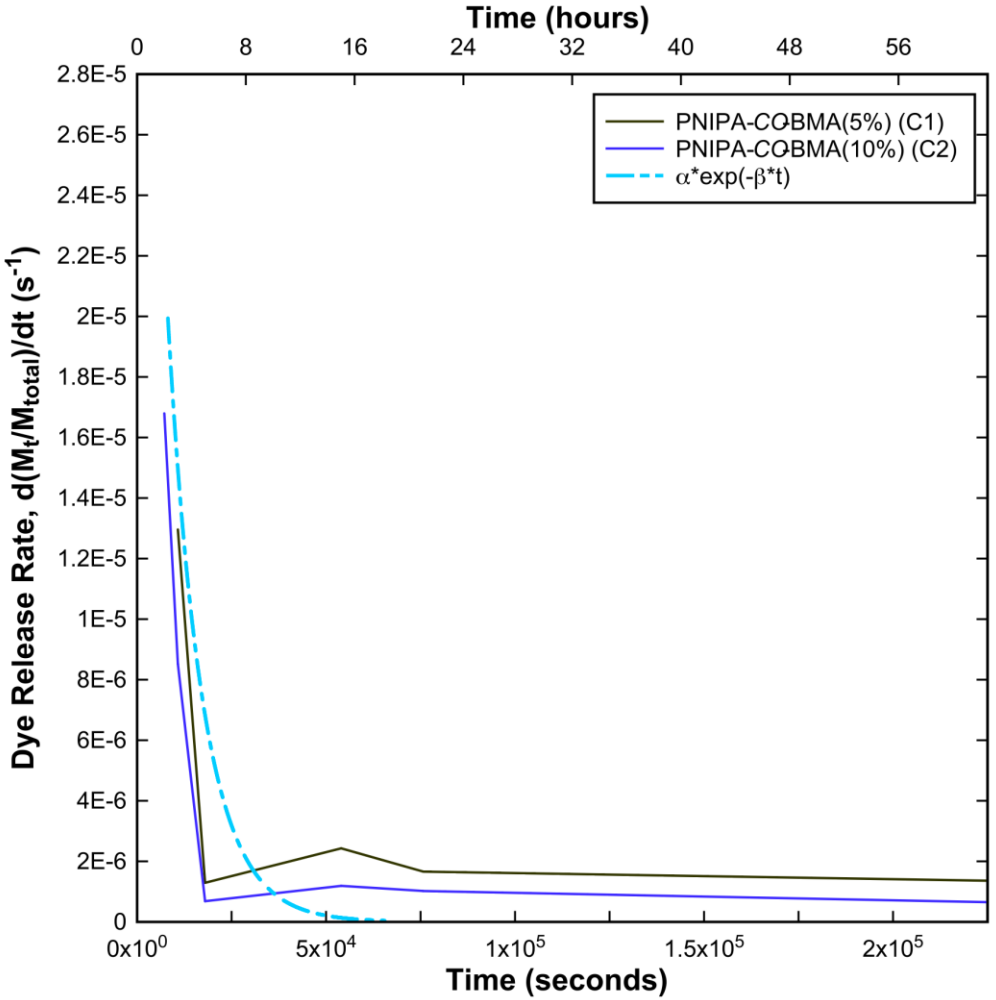


$$\frac{dM(t)}{dt} = \frac{8DM_{total}}{r^2}\exp\left(-\frac{D\pi^2 t}{r^2}\right)$$

Membrane release model

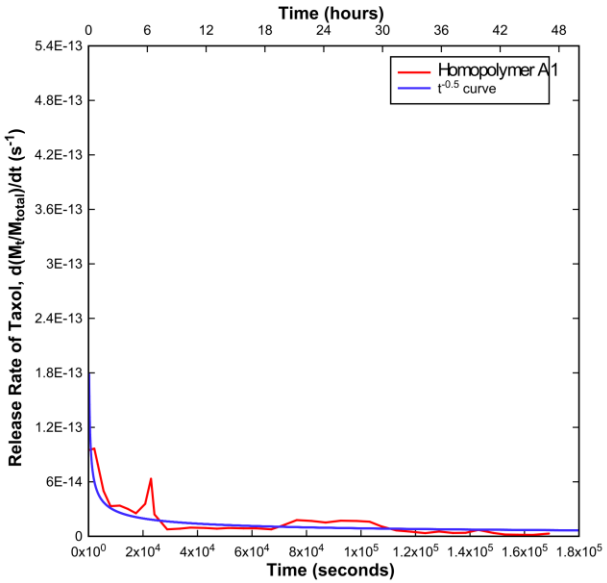
- **Hydrophobic Copolymer- Dense skin layer controls rate of drug release**

$$\frac{dM(t)}{dt} = \frac{V_m A_g P M_{total}}{V_g^2} \exp\left(\frac{A_g}{V_g} Pt\right)$$

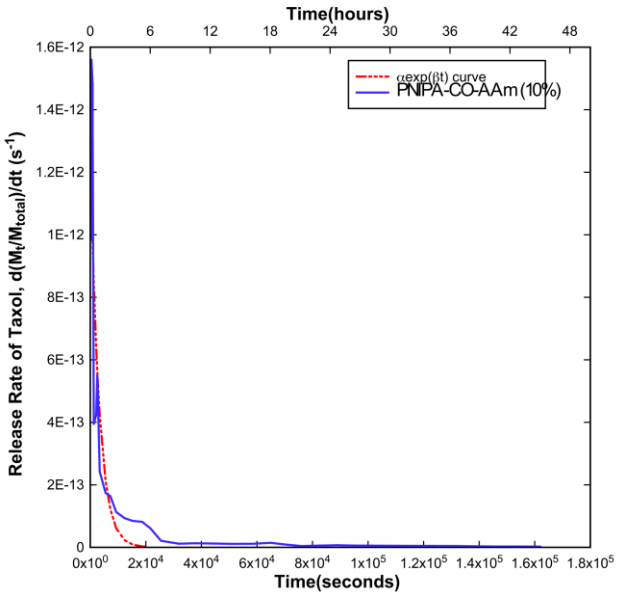


Paclitaxel Release Models

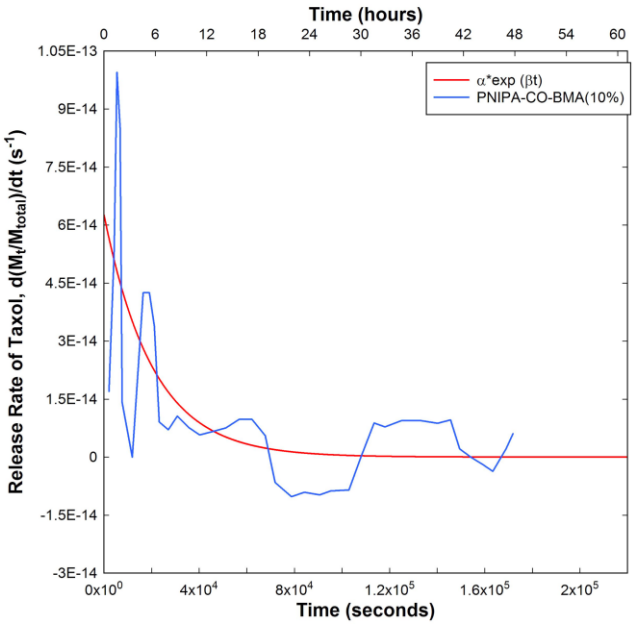
- **Paclitaxel release rates follow same models and fits**



Homopolymer



Hydrophilic copolymer



Hydrophobic copolymer

Temperature dependence of Diffusivities and Permeabilities

- **Release were fitted to equations to obtain diffusivity and permeabilities**
  - **Obtained for hyperthermic range**
  - **Fitted into Arrhenius equation to obtain Activation energies**
  - **Different properties before and after gel transition due to configurational differences**
  - **Higher hydrop** $\frac{dM(t)}{dt} = 2M_{total}\left[\frac{D}{\pi r^2 t}\right]^{\frac{1}{2}}$ **ıer**

$$\frac{dM(t)}{dt} = \frac{8DM_{total}}{r^2}\exp\left(-\frac{D\pi^2 t}{r^2}\right)$$

$$\frac{dM}{dt} = \frac{V_m A_g P M_{total}}{V_g^2}\exp\left(\frac{A_g}{V_g}Pt\right)$$

Gel Code	Gel Composition	Diffusivity or Permeability at Temperature (°C)			
		37	41	43	45
A1	PNIPA	1.68E-12 m^2/s	-	-	-
B1	PNIPA-co-AAm (95%-5%)	1.21E-9m^2/s	8.06E-10 m^2/s	1.41E-9 m^2/s	1.47E-9 m^2/s
B2	PNIPA-co-AAm (90%-10%)	6.33E-10 m^2/s	1.28E-9 m^2/s	7.21E-10 m^2/s	7.61E-10 m^2/s
C1	PNIPA-co-BMA (95%-5%)	1.73E-7m/s	2.51E-6 m/s	1.96E-6 m/s	2.55E-6 m/s
C2	PNIPA-co-BMA (90%-10%)	1.44E-7 m/s	2.10E-6 m/s	8.17E-7 m/s	1.12E-6 m/s

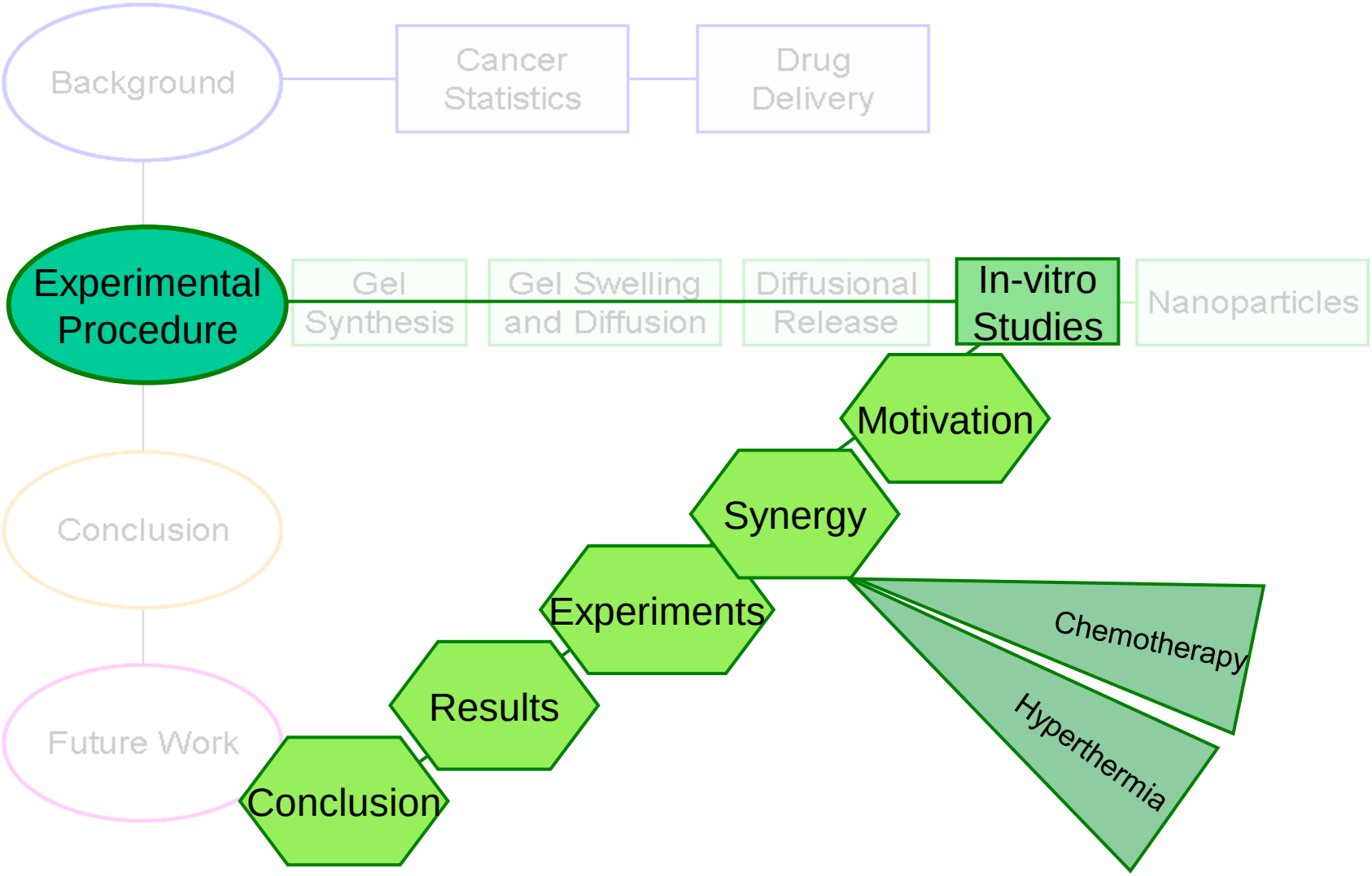
Gel Code	Gel Composition	Activation Energy (kJ/mol)
B1	PNIPA-co-AAm (95%-5%)	124.94
B2	PNIPA-co-AAm (90%-10%)	142.46 (before T_c)
		22.56 (after T_c)
C1	PNIPA-co-BMA (95%-5%)	275.48
C2	PNIPA-co-BMA (90%-10%)	198.72

For taxol:
Homopolymer: 2.38E-16m2/s
Hydrophilic: 6.33E-10m2/s
Hydrophobic: 9.97E-11m/s

Conclusions

- Measured temperature dependence of diffusivities and permeabilities can be used to control the release of cancer drugs
  - Activation energy ~ 120-140kJ/mol (Monolithic)
  - Activation energy ~ 200-275kJ/mol (Dense skin layer)
- Local release conditions controlled by T_c which is induced by heat trigger (Joule heating of gel)
- Control of T_c : Available Material Parameters
  - Copolymerization (amount and polarity of comonomer)
  - Gel size
  - Drug loading solution
- Micro-chip needed for actual control of drug release

Outline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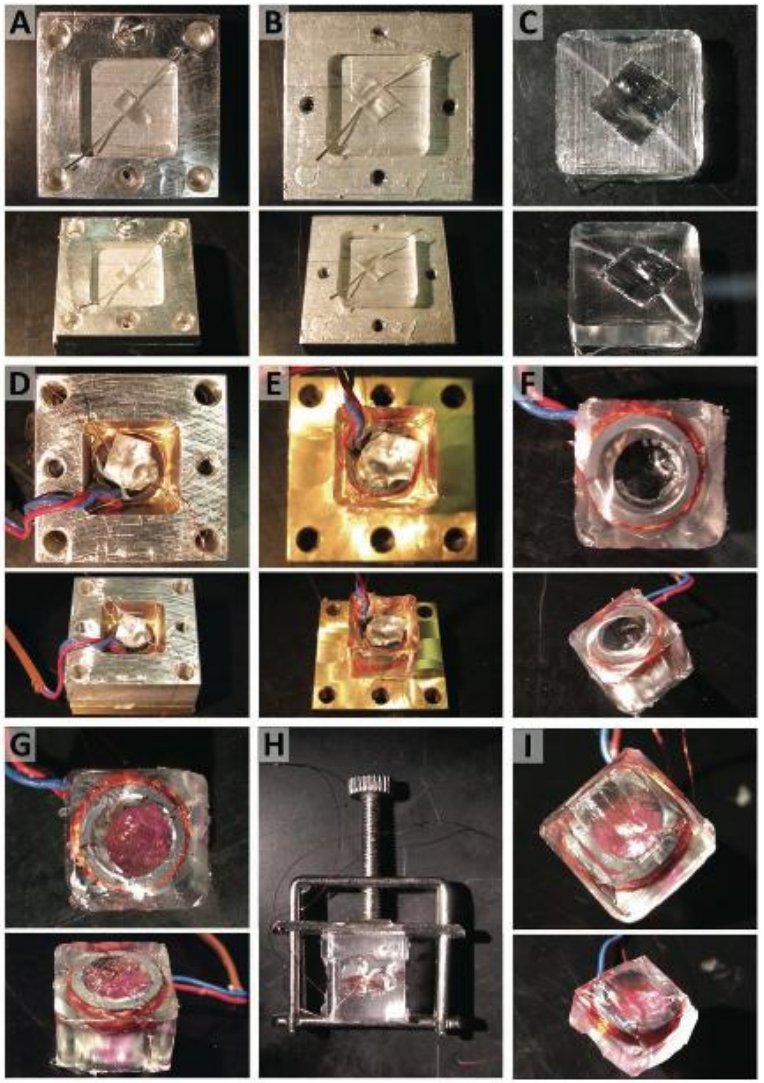
Motivation
Synergy
Experiments
Results
Conclusion
Chemotherapy
Hyperthermia

Motivation

- Drug release have been modeled
- Can help predict quantity of loading needed
- Naturally *in-vitro* and *in-vivo* work should follow
- Device Integration studies becomes important for final applications
- But first, what about the device?

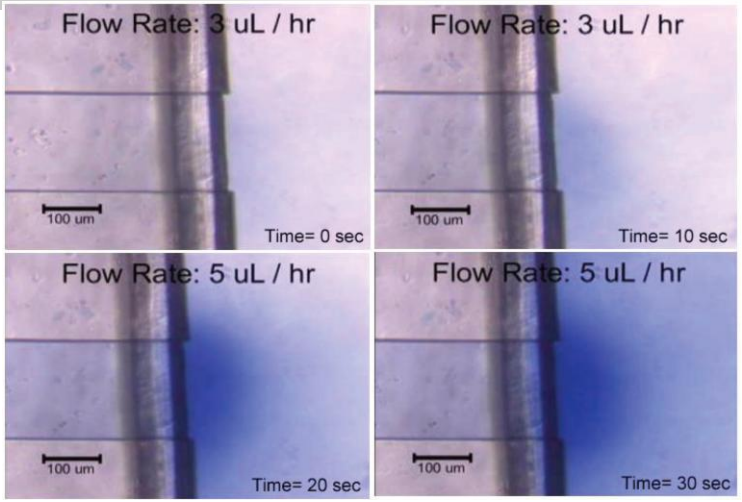
Device Making…

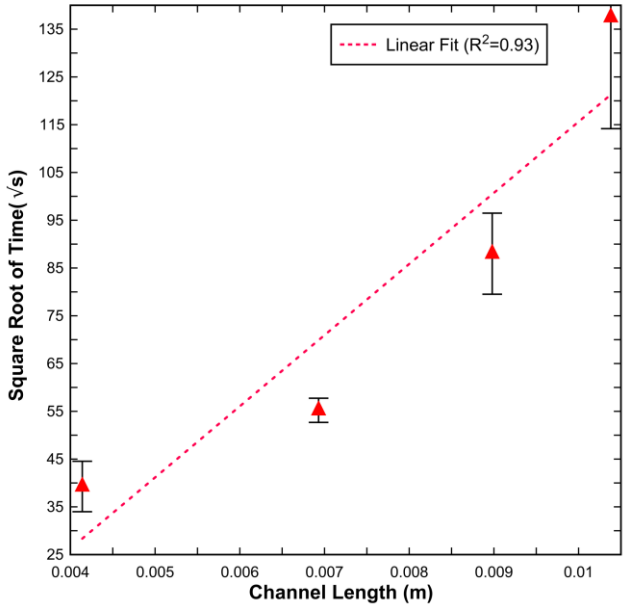
- **Molds made for PDMS polymer**
  - Caps for encapsulation unit made
  - Micro-wires inserted for channels
  - Main body for encapsulation
  - Thermocouple and heating coil inserted
  - Loaded gel placed in reservoir
  - Cap assembled to main body
  - Therapeutic unit finished



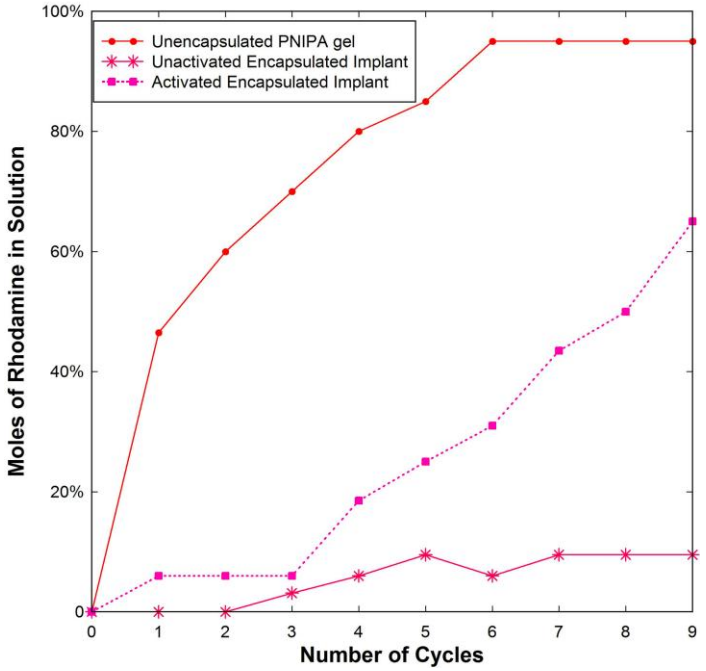
Drug Elution From Device...

- Proof of Concept
- Flow rates induced through center of device
  - Show flow out of device
  - Pressure can be induced internally
- PID-controlled temperature induced flow





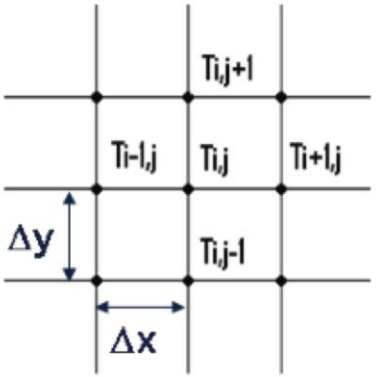
$$L \propto \sqrt{t}$$



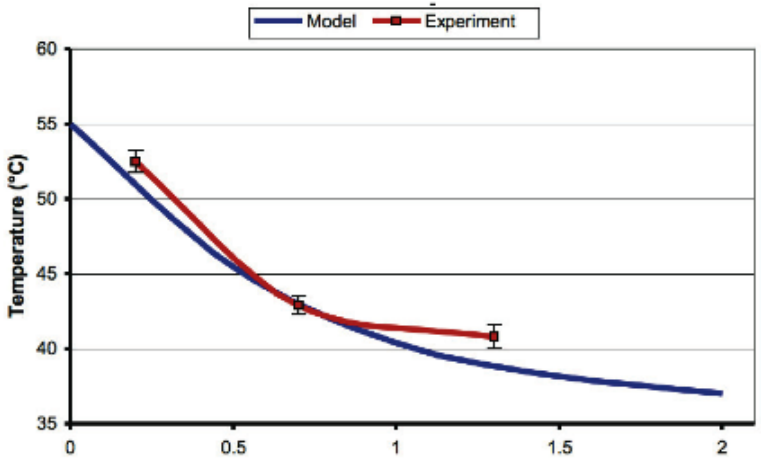
Hyperthermia: Predictions and Experiments

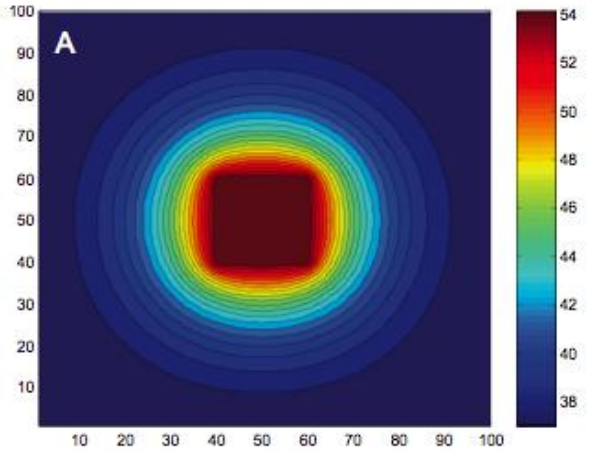
- **Fourier's law of heat conduction**
  - **Forward time central difference**

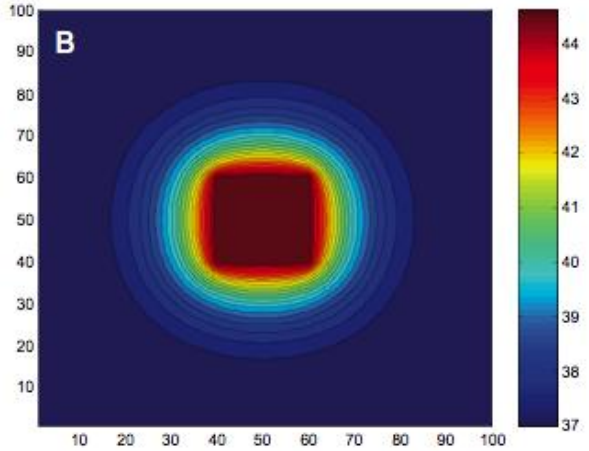
$$\frac{d^2T}{dx^2} + \frac{d^2T}{dy^2} + \frac{1}{k}g = \frac{1}{\alpha}\frac{dT}{dt}$$



100 nodes by 100 nodes





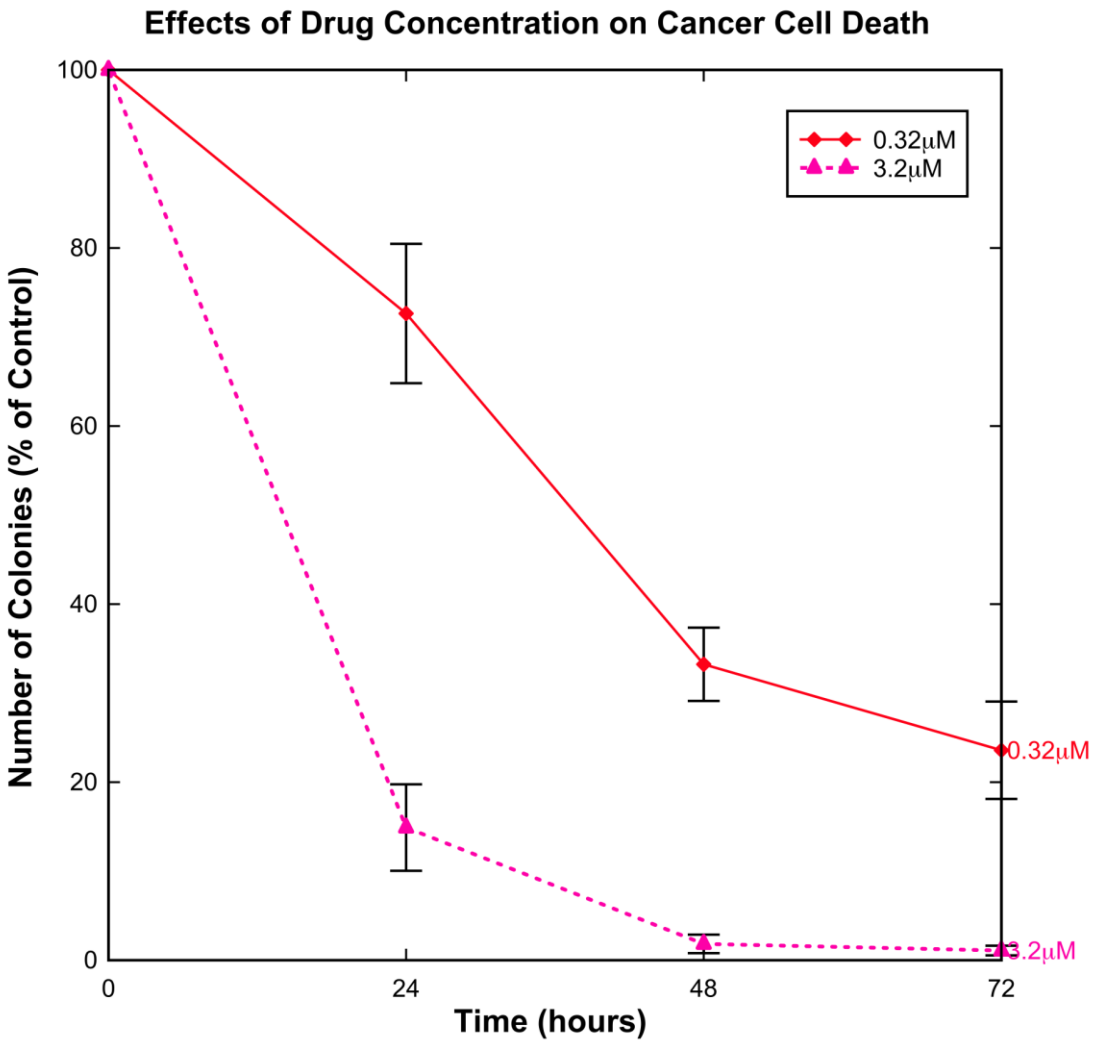


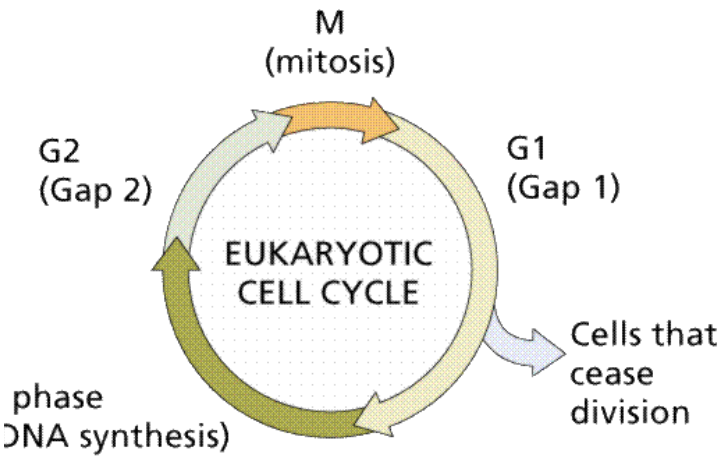
Modeling of the Thermal Diffusion of Heat from the Hyperthermia Device into its Surrounding. Using a MatLab program, the heat diffusion was projected in a static system until equilibrium was reached. The temperature isolines of the system were drawn at equilibrium condition. **A** shows the results for a system where the implant is set at 55°C and at 45°C in **B**. In both cases, the outside extremities were set to 37°C. *Scale: 10 unit = 0.5 cm*

Chemotherapy and Hyperthermia: A Synergy?

- Combination of therapies usually done
- Device introduced have the ability to achieve this
- Necessary to determine if synergy is achievable
  - What temperature might be needed to attain this?
  - What concentration of drug?
  - Hyperthermia causes restructuring of cytoskeletal network
  - Paclitaxel acts as a microtubule stabilizer that halts cytoskeletal responses
- Clonogenic assay protocols
  - Colonies are counted after days of treatment
  - Only viable cells form colonies

Preliminary Cell Experiments: Drug Alone



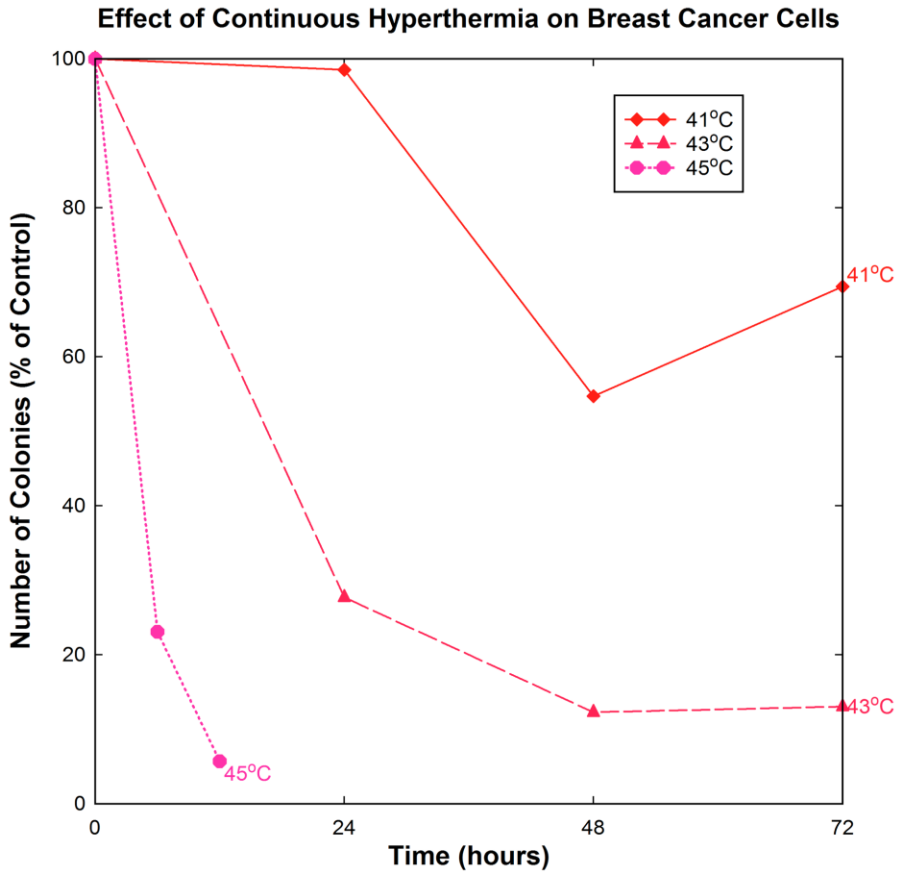


www.science.smith.edu/departments/Biochem/Chm…

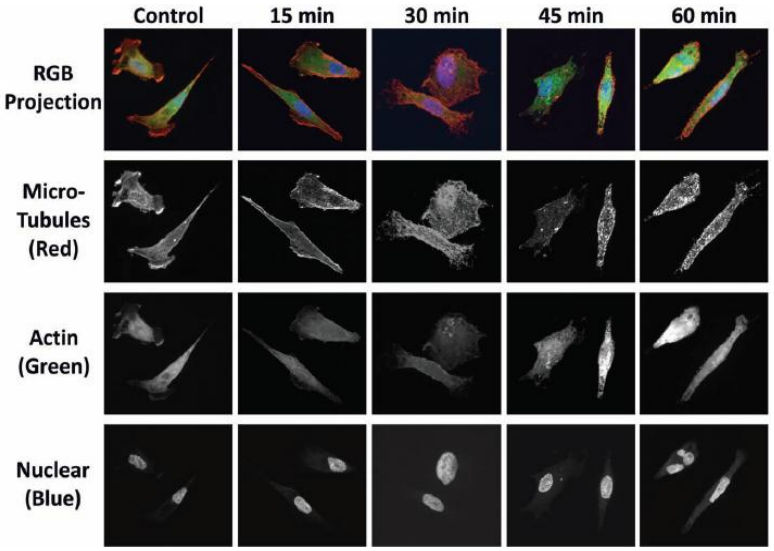
- Cause blockage in the late G2/M phase
- No effect if added at start of S phase

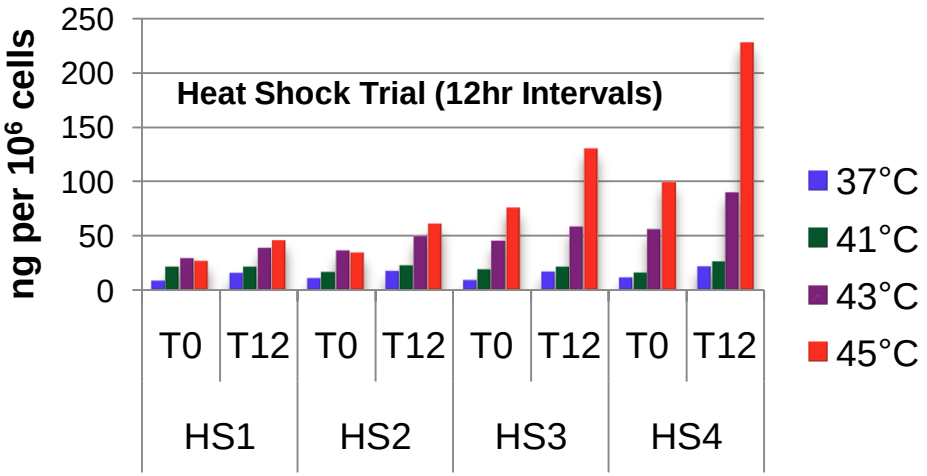
- Three concentrations were tested
- 32μM kills all cells within the first few hours

Preliminary Cell Experiments: Heat Alone



Cytoskeleton and membrane at 43C



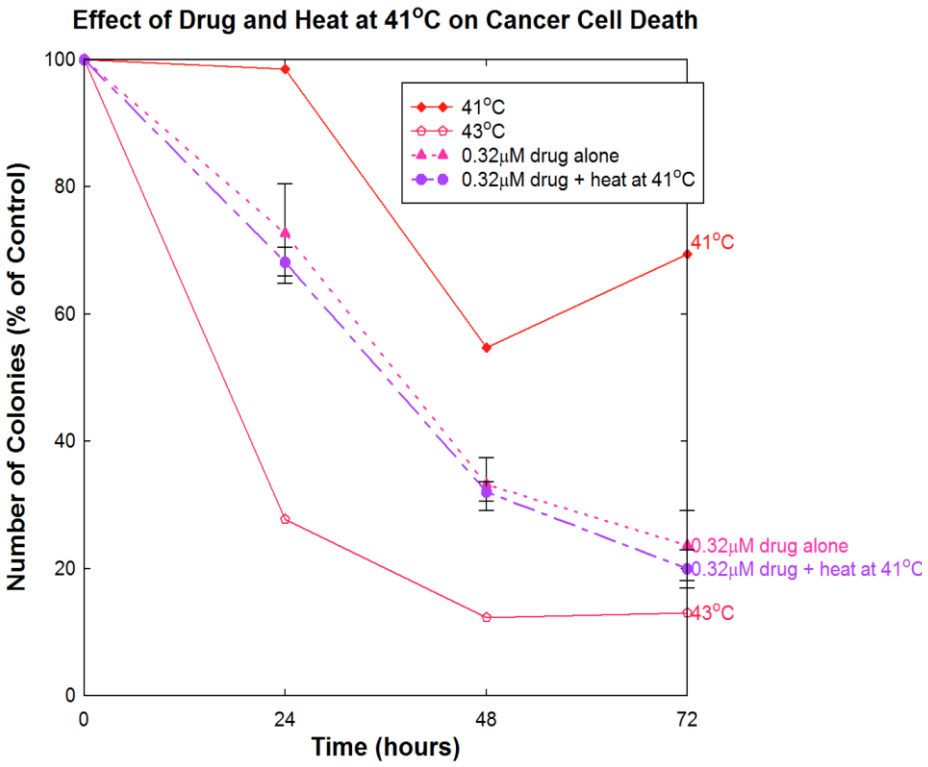


Extracellular release of HSP 70

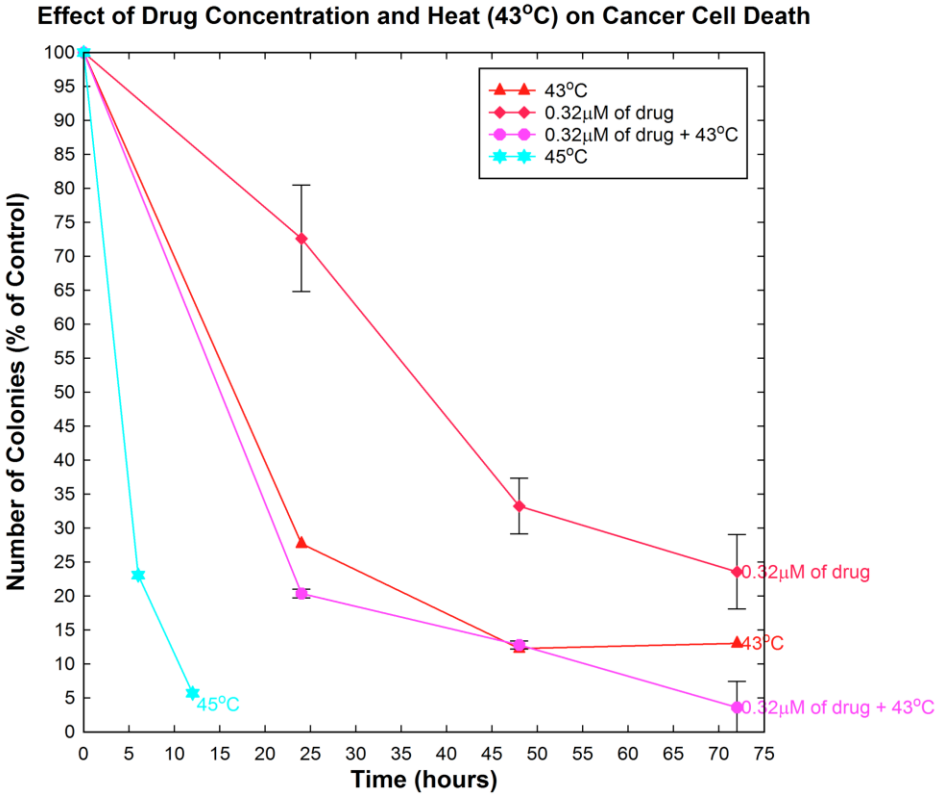
- 43C seen to be optimum, 45C results in necrosis
- Restructure of cytoskeleton observed
- Release of HSP 70 increase with temperature

Preliminary Cell Experiments: Synergistic Effect

Drug + Heat at 41°C



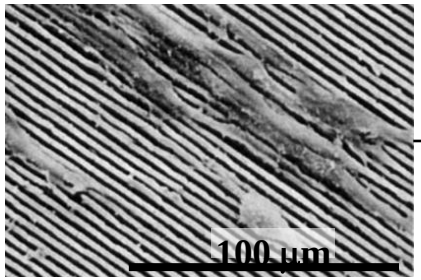
Drug + Heat at 43°C



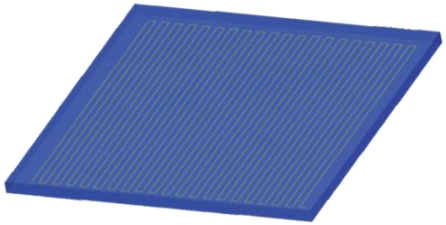
Reasons for Synergy

- Paclitaxel prevention of network restructure leading to shock, damaged membrane, and death
- Excessive release of HSP 70 aided by paclitaxel causing cell membrane breach and programmed cell death
- Synergy optimum at 43C and 0.32μM of paclitaxel

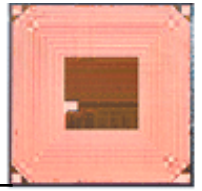
Localized Biomedical Device: An Innovation Through Integration



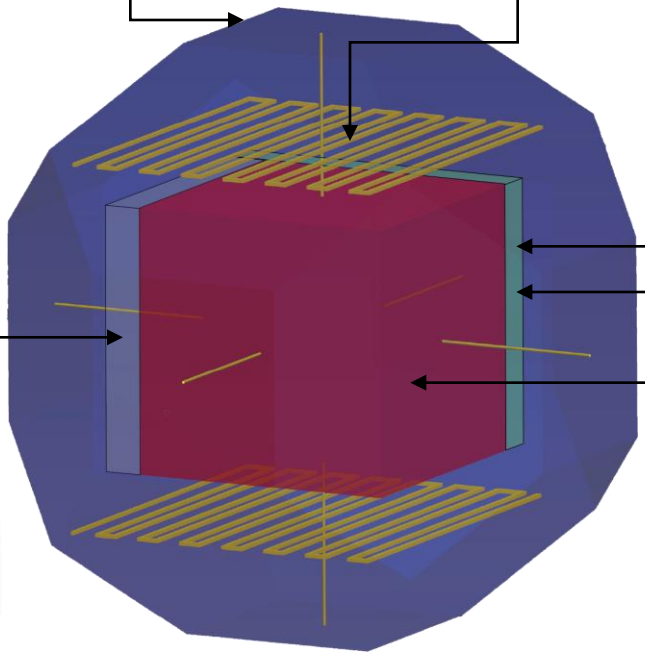
Surface Texture


Hyperthermia Device

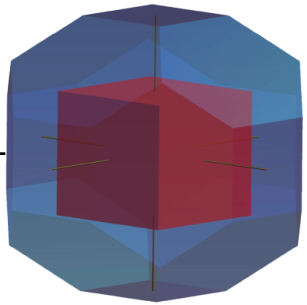
RFID Tag



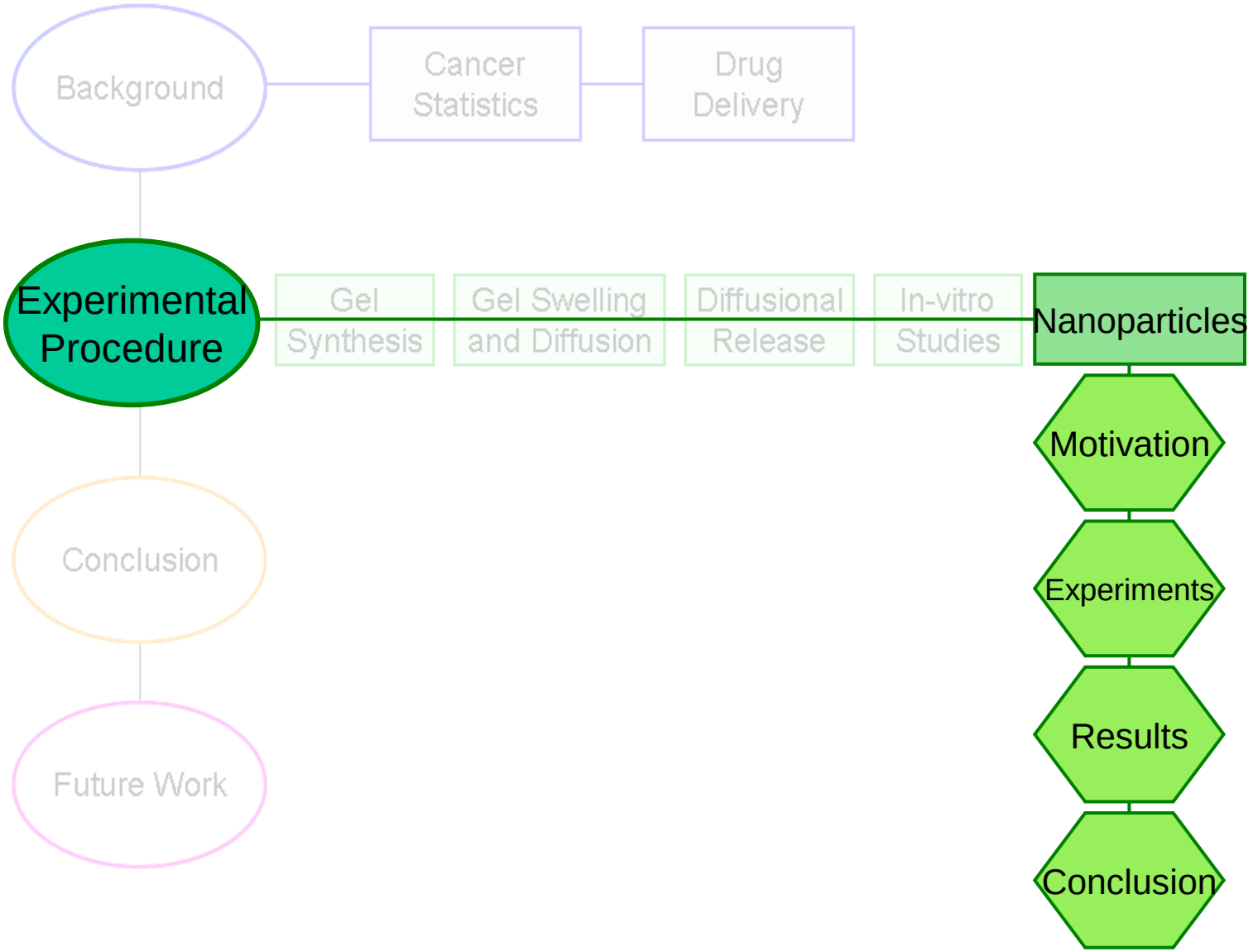
Battery


Multi-Modal Implant


Microprocessor


Drug Delivery Device

Outline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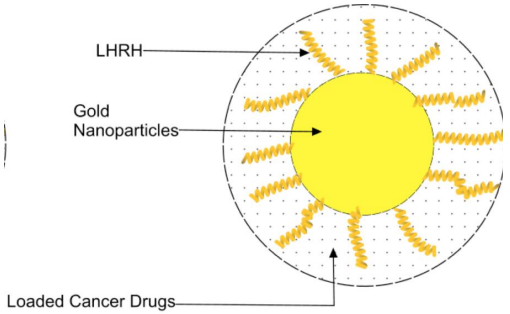
Conclusion
Future Work

Motivation

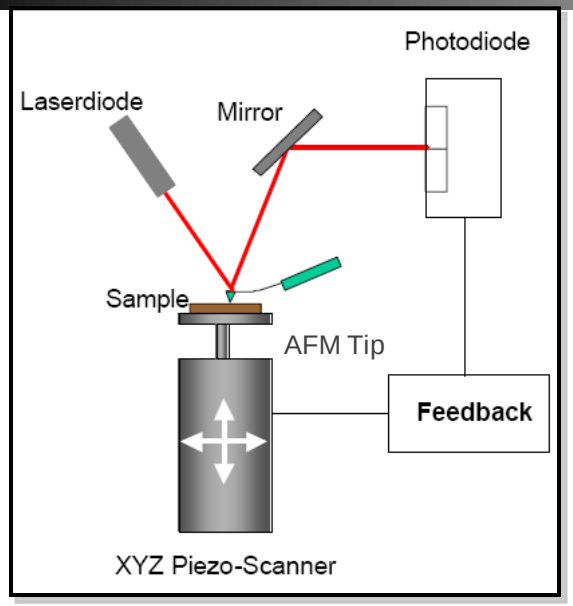
- **Previous section describes implantable delivery device**
  - **Designed for solid tumors after resection**
- **Nanoparticles present new ways of binding, detecting and killing cancer cells**
  - **Detection is of paramount importance**
  - **Multifunctional materials can kill cancer cells by heat and release of drug**
    - Gold and Iron oxide Nanoparticles
    - Nanocomposite structures
      - Gold (imaging core) with heat
      - Encapsulated drug
      - Molecular recognition units
      - Binder/Linkage chemistry
      - Protective coatings
  - **Robustness of such systems important**
    - No adhesion work has been done in this regard

Stage	Five-Year Survival Rate (%)			
	Breast	Ovarian	Stomach	Lung
I(A)	100	93	78	47
II(A)	92	79	58	26
III(A)	67	51	20	8
IV(A)	20	17.5	8	2

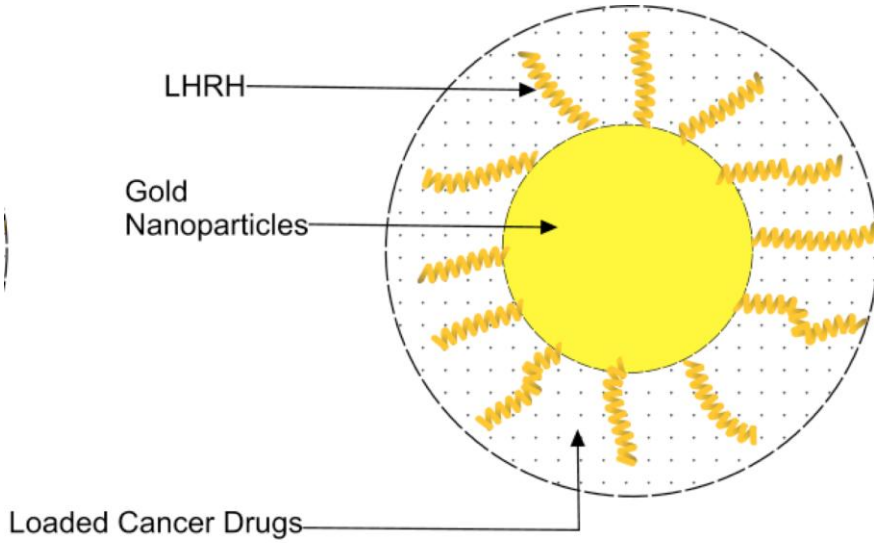
• From first stage of diagnosis (Melancon et al, 2009)



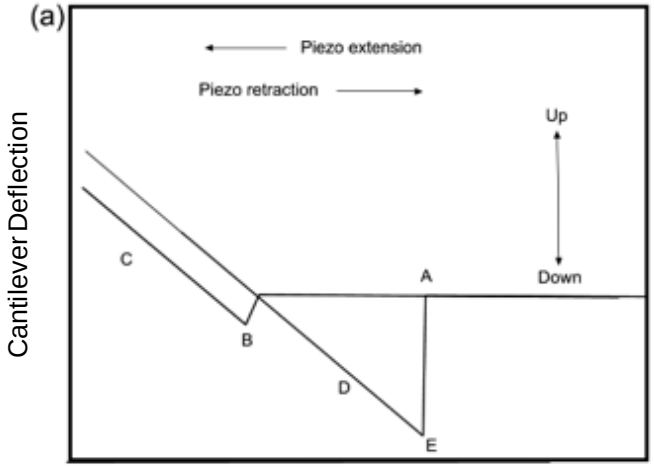
AFM Mechanics: Adhesion Force

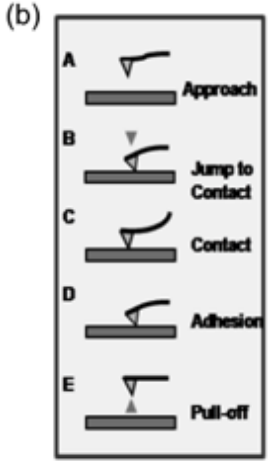


AFM Setup

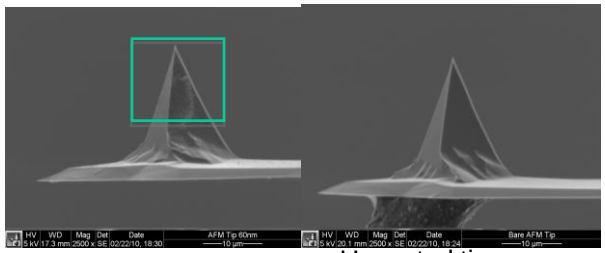


Coating on Tip	Substrate
Taxol	Gold
LHRH	Gold
Antibody	Gold
Antibody	Taxol
LHRH	Taxol





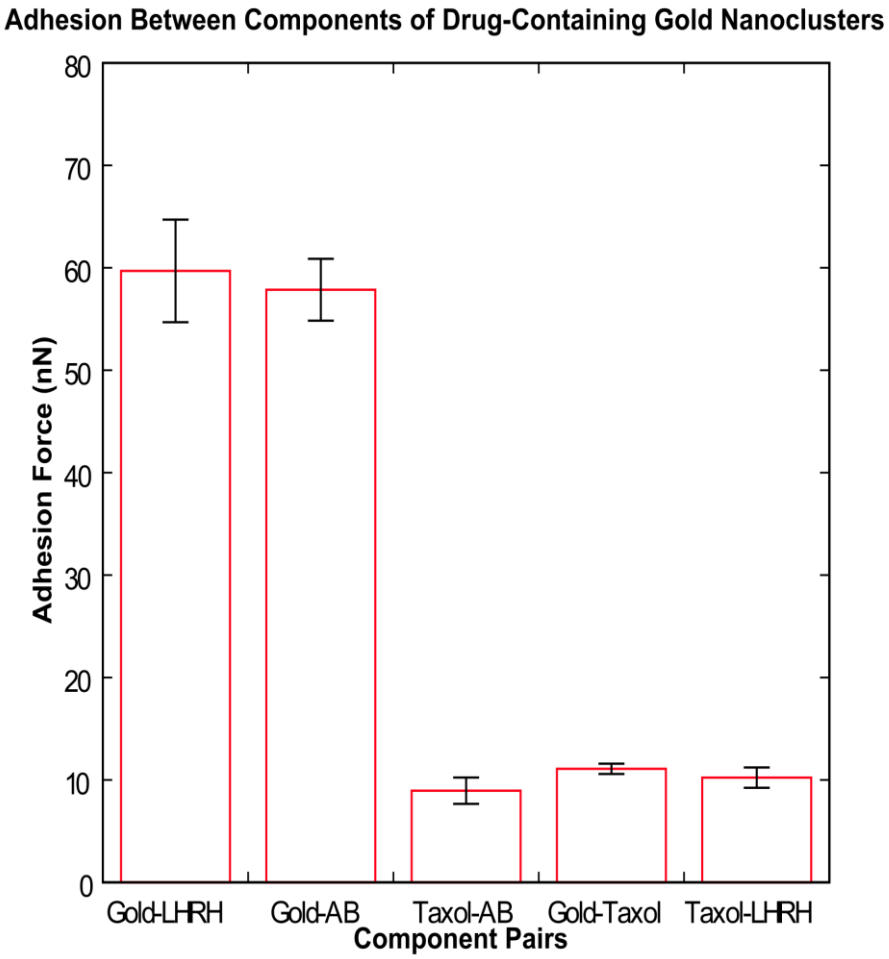
Hooke's Law $F = -k_c \times d_c$



Coated tip Uncoated tip

It's all about the drug!

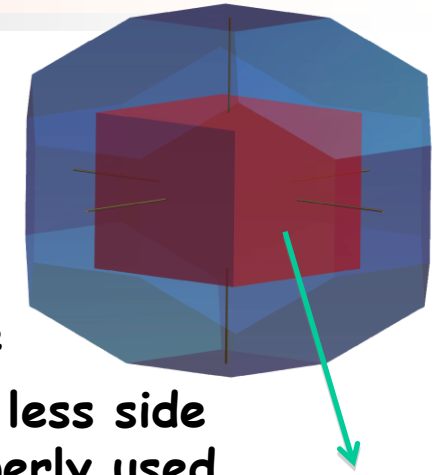
- **Results suggest that weakest adhesive interactions involve the drug**
  - **Implies strong cohesive bonds for paclitaxel**
  - **Robustness of systems will depend on drug-components interactions**
  - **Careful engineering needed to prevent unintentional drug release**



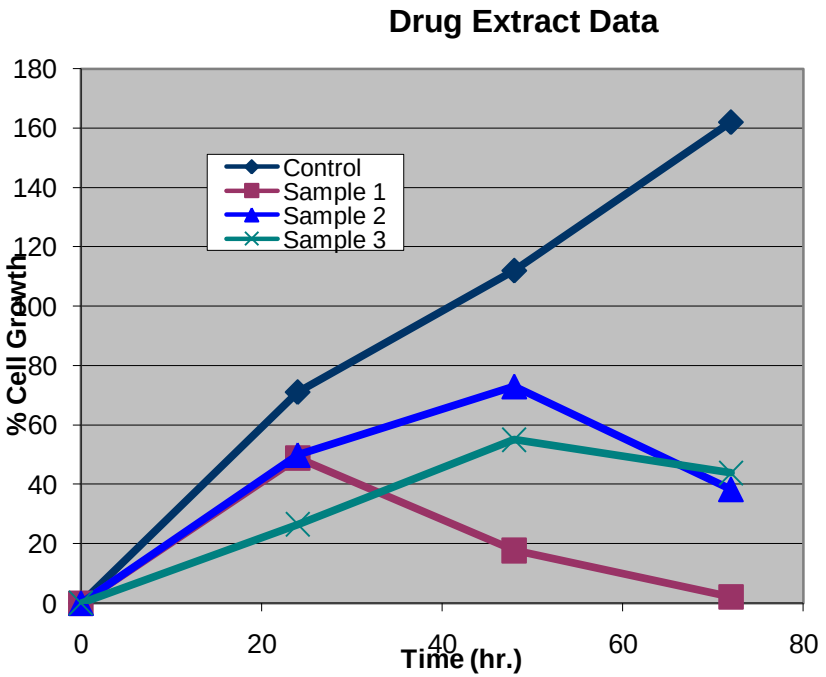
The Potential Integration of African Plant Extracts

- African plants could be loaded in implants.
  - Paclitaxel, from Taxus brevifolia
  - Sutherlandia frutescens. Kankerbos in Afrikaans, cancer bush in English
  - Cajanus cajan, Parquetina nigrescens, and Terminalia catappa currently being under studied by the Soboyejo group - Results so far are promising.

- Merits
  - Time-tested
  - Cheap
  - Easily available
  - Less toxic and less side effects if properly used



Plant extracts



Summary and Concluding Remarks

- Hydrogels provide a practical method of storing fluids/cancer drugs and “pumping” through micro-channels to the target tissue or organs
- Diffusion through the gels were predominantly non-fickian but were found to be well described by simple monolithic and membrane models
- Embedded heating element inadvertently cause further therapeutic treatment through local hyperthermia
- In-vitro studies show 43C and 0.32μM as the optimum conditions for synergy
- Consequently, a multi-modal device with capability of drug release and hyperthermia was presented

Summary and Concluding Remarks

- In-vitro and in-vivo studies are needed to explore the possibility of synergistic cancer treatment effects with the device
- In in-vivo studies, heat may be generated using alternating magnetic fields, radio frequency waves or rechargeable batteries as in pacemakers
- Finally, AFM can be used to study adhesion forces for drug-conjugated nanoclusters
- In such systems where synergy is achievable, robustness depends largely on all other components interactions with the drug.

Suggestions for Future Work

- **Improving the mechanical properties of the gels**
  - Largely limits their applications in drug delivery
  - IPN can be used but with adequate release characteristics
  - Creep and Visco-elastic properties should also be studied
- ***In-vitro* and *In-vivo* studies using the device**
  - Work done was to show proof of concept
  - Needed to confirm mechanism in a way that allows programming
  - Miniaturization of the device needed for *in-vivo* studies
- **Understanding the underlying mechanisms of synergy**
  - Provided synergy in terms of structural changes
  - What is the effect of treatment schedule? Heat before drug or vice-versa. What is the effects of simultaneous application of heat and drug?
- **Nanoparticles composites for drug delivery and hyperthermia**
  - Explore the interactions between gold and laser beams for heat generation
  - Basis for synergy and provides possibility of molecular scalpels in surgeries
  - What will be the effects of liquid or medium on the adhesion forces measured?

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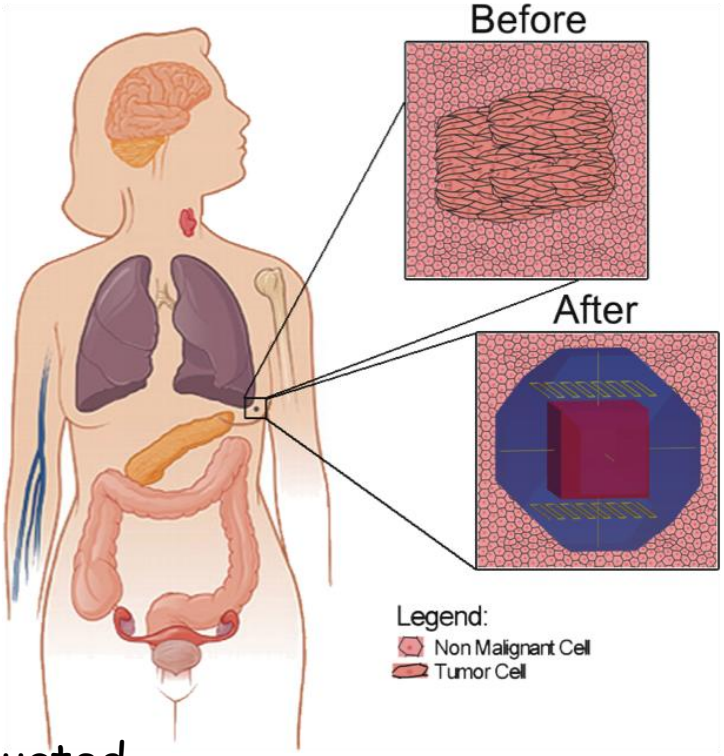
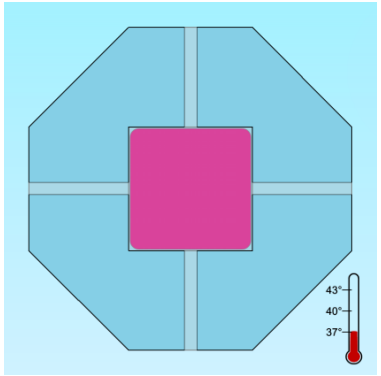
Thank you

Questions?

Multi-modal Implant for synergistic Cancer Treatment

- Solid tumors: Localized delivery from implanted device with heat and drug release
- Controlled delivery to the site of action
  - Smaller dose required
  - Higher efficacy
  - Reduced side effects





- Hyperthermia and heat-actuated polymer
- Resistive heating and hydrogel
- PDMS encapsulation
- Machined for tissue integration
- Microchannels for release