Harnessing the antitumor immune response with laser immunotherapy

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Laser immunotherapy

Work by WR Chen with a photodynamic therapy variant.

Goal: Thermal destruction of primary tumor via laser, combined with stimulated immune response to find and kill *otherwise untreated* metastases.

Modified from Chen (2011).

Project Motivation

Build model(s) to propose mechanism for antitumor immune activity set in motion by laser immunotherapy (LIT).

Long-term hopes:

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Build model(s) to propose mechanism for antitumor immune activity set in motion by laser immunotherapy (LIT).

Long-term hopes:

- elucidate immune mechanisms, key steps
- explain outcome time-scales
- optimize treatments
- predict outcomes

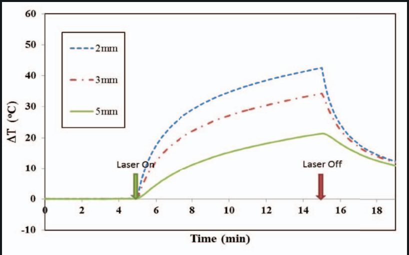
Animal models and application

- typically young rats with DMBA-4
  (aggressive, transplantable, metastatic mammary tumor cells)
- cell cultures, and recently mice
- now inducible pancreatic cancer

Partial treatment with no other option human patients (melanoma, breast)

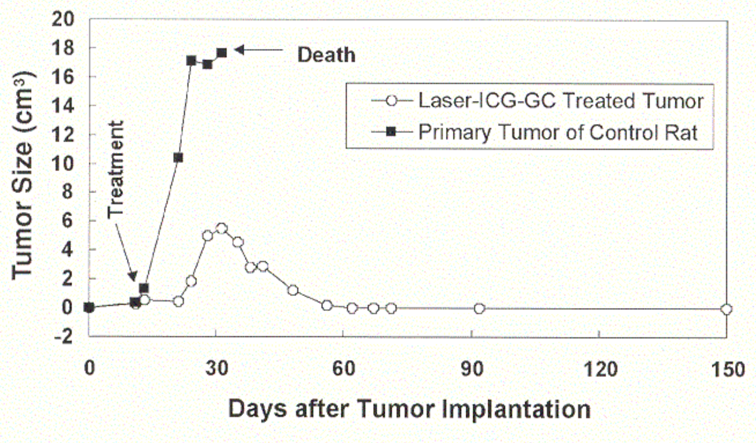
Experimental treatment plan

- inject $\approx 10^5$ tumor cells
- treatment at $\approx 10 - 14$ days
  - inject photothermal dye (locally absorbs laser energy, increases heat)
  - inject glycated chitosan (collaborators' patented immunostimulant – GC)
  - apply 5 min laser irradiation
- monitor tumor volumes, health ($\approx 30 - 100$ days PI)



Modified from Chen (2011).

Motivating data



Modified from Chen (2003).

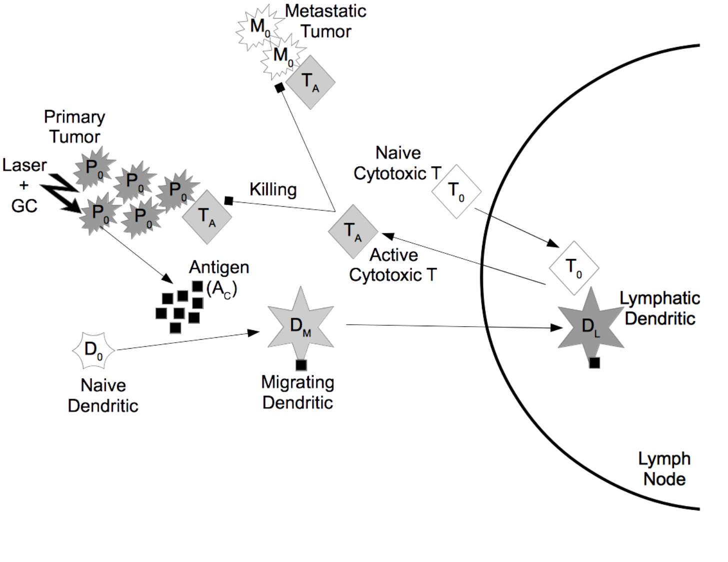
Immune Glossary

Consider a restricted subset of cell types and functions in this model:

- Cancer/tumor - primary (site of treatment and immune action)
  metastases (site of immune action)
- Dendritic cells - collect and present tumor antigen
- Cytotoxic T cells - kill tumor cells
- B cells - produce antitumor antibodies
- Helper T cells - 'help' other cells mature and function

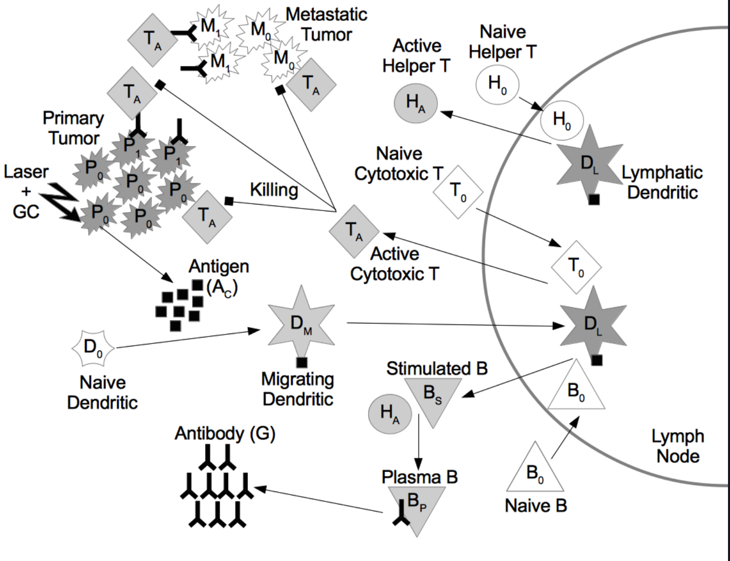
Additionally, we track antigen and antibody.

Conceptual Models



Modified from Chen (1997).

Conceptual Models



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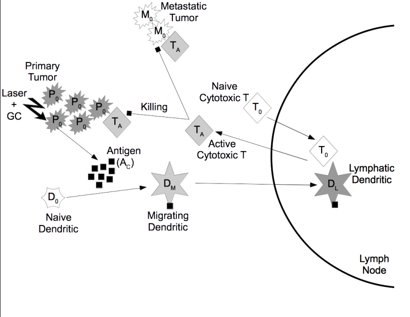
Mathematical Model

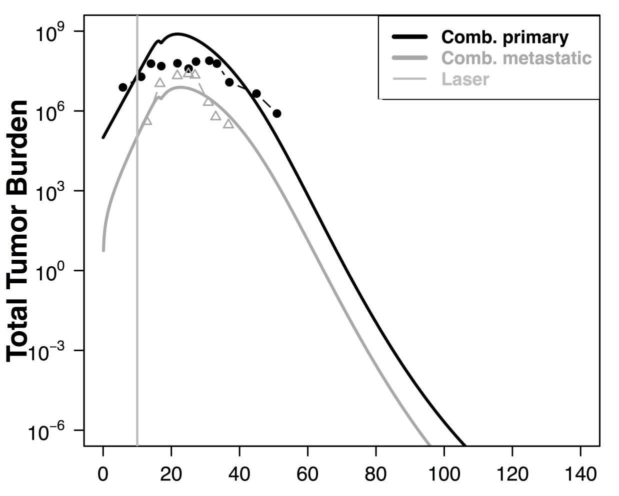
$$\frac{dD_0}{dt} = \sigma_d - \alpha A_c D_0 - \delta_{D_0} D_0$$
$$\frac{dD_m}{dt} = \varepsilon_m \alpha A_c D_0 - \eta D_m - \delta_{D_m} D_m$$
$$\frac{dD_\ell}{dt} = \varepsilon_\ell \eta D_m - \delta_{D_\ell} D_\ell$$
$$\frac{dT_0}{dt} = \sigma_t - \beta D_\ell T_0 - \delta_{T_0} T_0$$
$$\frac{dT_c}{dt} = \nu_c \beta D_\ell T_0 - k \delta_{T_0} T_c$$
$$\frac{dC_p}{dt} = \gamma_p C_p - \mu C_p - \phi(t) C_p - \lambda_p T_c C_p$$
$$\frac{dC_m}{dt} = \sigma \mu C_p + \gamma_m C_m - \lambda_m T_c C_m$$
$$\frac{dA_c}{dt} = \rho \phi(t) C_p + \rho(\lambda_p T_c C_p + \lambda_m T_c C_m) - \omega A_c - \alpha D_0 A_c$$



Approach

1. Numerical solutions in **R**
2. Latin Hypercube Sampling
3. RMSE comparisons to data for illustration (no fitting procedure)
4. Regressions to spot trends between model parameters and measured model outcomes

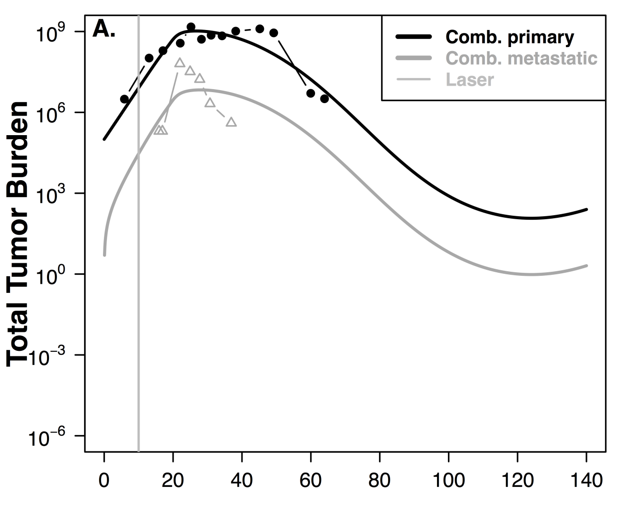
Sample results and animal data: Control



*vertical bar at $t = 10$: treatment time

Data from Chen (2003).

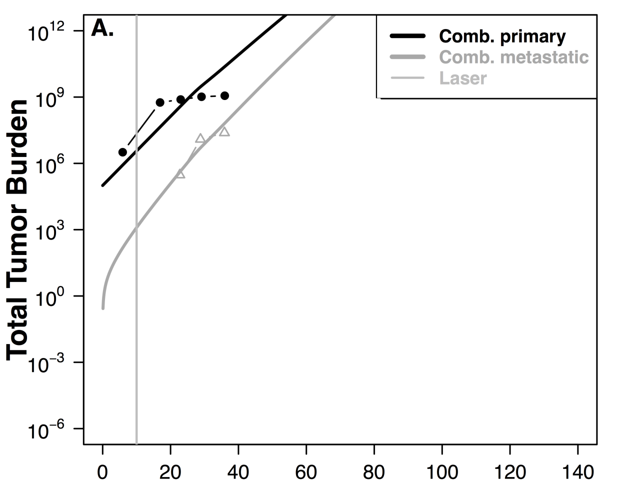
Sample results and animal data: Recurrence



*vertical bar at $t = 10$: treatment time

Data from Chen (2003).

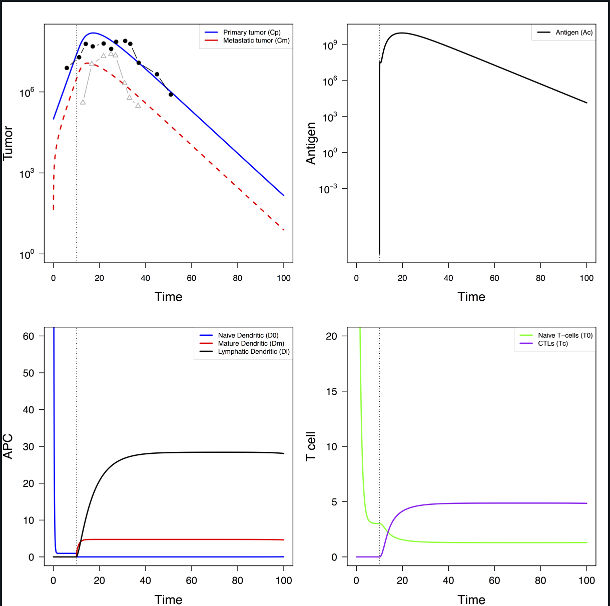
Sample results and animal data: Escape



*vertical bar at $t = 10$: treatment time

Data from Chen (2003).

Sample immune dynamics: Control



Broad simulation outcomes

Simulation summary:

- Initial treatment success: 866
- Initial treatment failure: 134

$n = 1000$ sampled parameter sets.

Trends in initial treatment failure:

- low CTL rates
- increased cell death rates
- increased tumor proliferation rates

Broad simulation outcomes

Simulation summary:

- Initial treatment success: 866
  - Complete clearance: 362
  - Recurrence: 477
- Initial treatment failure: 134

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  - naive supply, σ_c
  - proliferation, ν_c
- increased cell death rates
  - in lymphatic dendritic cells
  - in naive T cells
- increased tumor proliferation rates

Laser-GC consequences

Two other parameters:

- naive dendritic cell antigen collection efficiency, ϵ_m
- naive CTL activation rate by lymphatic dendritic, β

tended to be reduced in failed treatments.

We view as direct consequence of GC immunostimulation.

Future work

- Less model, More data?
  - Practical
    - parameter identification and scaling
    - coding/parameterizing treatment (laser–induced cell death)
  - Modeling
    - modeling cytokine activity
    - modeling memory cell activity
- Interpretation and analysis
  - incorporating immune cell data
  - inferring patient survivorship from tumor burden

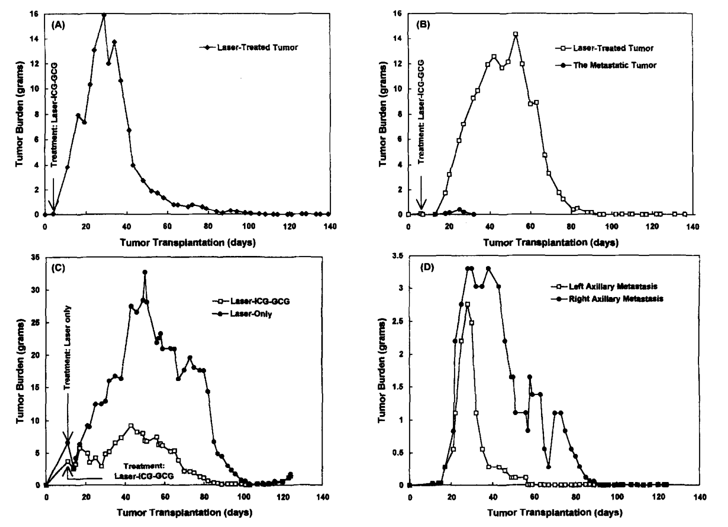
Big questions: Antigen and antibody

- Specific antigen(s) currently unknown – HSPs and what else?
- What about tumor/tumor environment is being targeted by antitumor immune response.

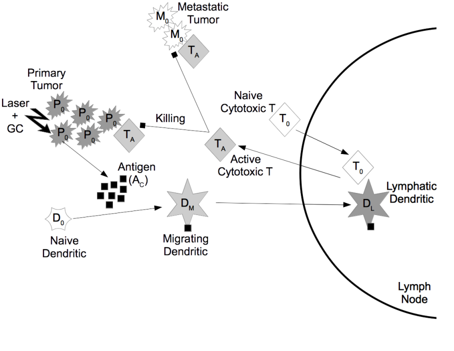
Big questions: Tumor microenvironment

- Pro-tumor macrophages and Tregs
- Current work with cyclophosphamide (CY) a Treg suppressor
- Modeling consequences (questions)
  - Does antibody target tumor cells to increase killing?
  - If so, who does the deed?
  - Or, does antibody target tumor associated immune cells?

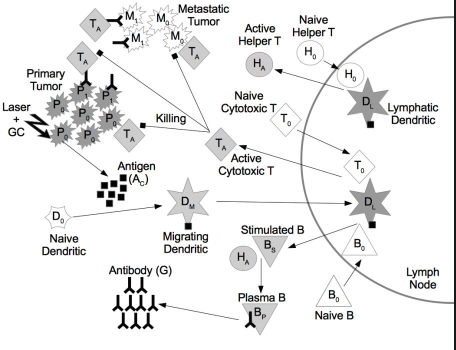
Big questions: Tumor burden



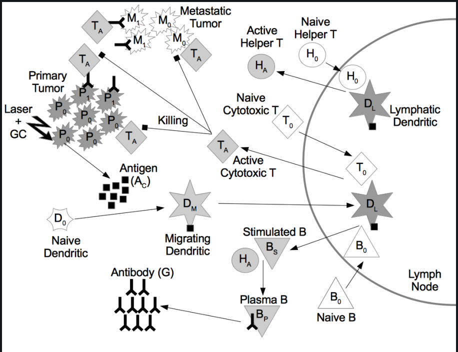
- model tracks tumor cell burden (scaled to volume)
- primary tumor burden contains scar tissue



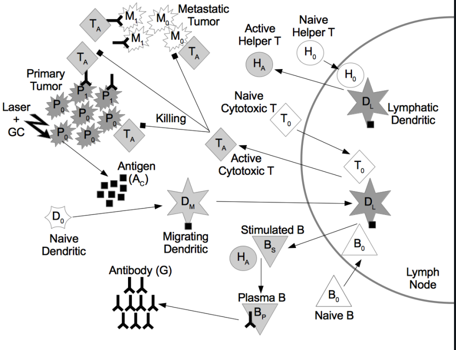
Metastatic
Tumor
M_0
M_0
T_A
Primary
Tumor
Laser
+
GC
P_0
P_0
P_0
P_0
P_0
T_A
Killing
Naive
Cytotoxic T
T_0
T_A
Active
Cytotoxic T
T_0
Antigen
(A_C)
Lymphatic
Dendritic
D_M
D_L
D_0
Naive
Dendritic
Migrating
Dendritic
Lymph
Node

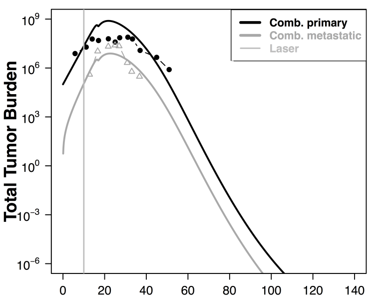


Metastatic Tumor
Active Helper T
Naive Helper T
Primary Tumor
Laser + GC
Killing
Naive Cytotoxic T
Lymphatic Dendritic
Active Cytotoxic T
Antigen (A_C)
Naive Dendritic
Migrating Dendritic
Stimulated B
Antibody (G)
Plasma B
Naive B
Lymph Node



$$
\begin{aligned}
\text{Naive Dend} \quad \frac{dD_0}{dt} &= s_d - \alpha A_c D_0 - \delta_{D_0} D_0 \\
\text{Migra Dend} \quad \frac{dD_m}{dt} &= \epsilon_m \alpha A c D_0 - \eta D_m - \delta_m D_m \\
\text{Lymph Dend} \quad \frac{dD_\ell}{dt} &= \epsilon_\ell \eta D_m - (k_1(\beta T_0 + b B_0 + \psi H_0) - \delta_\ell) D_\ell \\
\text{Naive Cyto T} \quad \frac{dT_0}{dt} &= s_t - \beta D_\ell T_0 - \delta_{T_0} T_0 \\
\text{Cyto T} \quad \frac{dT_c}{dt} &= \epsilon_c \beta D_\ell T_0 - k_2 \delta_{T_0} T_c
\end{aligned}
$$





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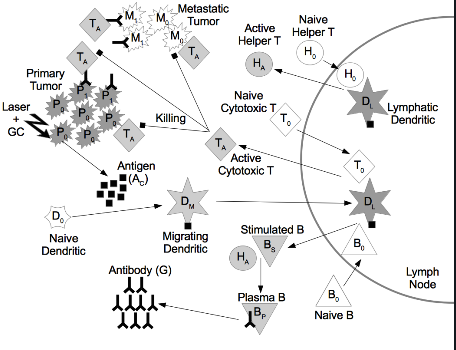

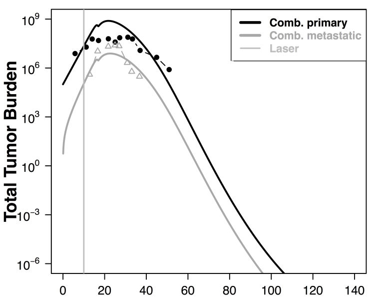

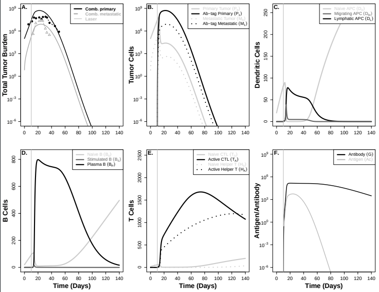

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Mathematical Model

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\end{aligned}
$$

$$
\begin{aligned}
\text{Naive Help T}\ \frac{dH_0}{dt} &= s_h - (\xi B_m + \psi D_\ell) H_0 - \delta_{H_0} H_0 \\
\text{Activ Help T}\ \frac{dH_a}{dt} &= \epsilon_a (\xi B_m + \psi D_\ell) H_0 - \delta_{H_a} H_a \\
\text{Naive B}\ \frac{dB_0}{dt} &= s_b - b B_0 D_\ell - \delta_{B_0} B_0 \\
\text{Stim B}\ \frac{dB_s}{dt} &= \epsilon_s b B_0 D_\ell - \tau H_a B_s - \delta_{B_s} B_s \\
\text{Mature B}\ \frac{dB_m}{dt} &= \epsilon_m \tau H_a B_s - \delta_{B_m} B_m
\end{aligned}
$$

$$
\begin{aligned}
\text{Antitumor Ab}\ \frac{dG}{dt} &= \delta_G G - \theta(P_0 + M_0) G \\
\text{Tumor Ag}\ \frac{dA_c}{dt} &= \rho\phi(t) P_0 + p T_c(\lambda_0 P_0 + \lambda_0 M_0 + \lambda_1 M_1 + \lambda_1 P_1) - \omega A_c - \alpha A_c D_0 \\
\text{Primary}\ \frac{dP_0}{dt} &= (1-\mu)\gamma_p (P_0 + \epsilon_x P_1) - (\phi(t) + \theta G + \lambda_0 T_c + \delta_P) P_0 \\
\text{Ab-tag Primary}\ \frac{dP_1}{dt} &= (1-\epsilon_x)(1-\mu)\gamma_p P_1 + \epsilon_G \theta G P_0 - (\lambda_1 T_c + \delta_P) P_1 \\
\text{Metastatic}\ \frac{dM_0}{dt} &= \gamma_m (M_0 + \epsilon_x M_1) + \sigma\mu\gamma_p (P_0 + \epsilon_x P_1) - (\theta G + \lambda_0 T_c + \delta_M) M_0 \\
\text{Ab-tag Metastatic}\ \frac{dM_1}{dt} &= (1-\epsilon_x)\gamma_m M_1 + (1-\epsilon_x)\sigma\mu\gamma_p P_1 + \epsilon_G \theta G M_0 - (\lambda_1 T_c + \delta_M) M_1
\end{aligned}
$$