Mathematical Assessment of Oncolytic Virotherapy

Ilyssa Summer

June 9, 2015
Cancer Therapies

Cancer is a complex collection of diseases involving unregulated cell growth. Common treatments include:

- Surgery
Cancer Therapies

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- Surgery
- Radiation therapy
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- Immunotherapy
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- Surgery
- Radiation therapy
- Chemotherapy
- Immunotherapy
- Targeted Therapy
Oncolytic Virus

- "Anti-cancer" Oncolytic virus is type of Virotherapy
  - Viral gene therapy
  - Viral Immunotherapy
- Virus that selectively infect and kill cancer cells
Oncolytic Virus

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  - Viral gene therapy
  - Viral Immunotherapy
- Virus that selectively infect and kill cancer cells
Milestones in Oncolytic Virotherapy


Clinical Trials - Phase 2 Oncovex (2009), Viremic threshold (2011)

Russell et al, 2012
Clinically tested Oncolytic Viruses

- adenovirus

- reovirus

- measles

- herpes simplex (HSV)

- Newcastle disease virus
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- adenovirus
- reovirus
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Recent Experiments

Modified herpes virus therapy shows promise in melanoma

The Pharmaceutical Journal, 5 JUN 2015 | By Joanna Lyford
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**Nature Reviews Drug Discovery | News and Analysis**

**Oncolytic viruses get a boost with first FDA-approval recommendation**

Elie Dolgin

Published online 01 June 2015

The future of cancer-killing viruses lies in their potential to augment cell and antibody immunotherapies.
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*NATURE REVIEWS DRUG DISCOVERY | NEWS AND ANALYSIS*

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Elie Dolgin

Published online 01 June 2015

The future of cancer-killing viruses lies in their potential to augment cell and antibody immunotherapies.

The HDAC Inhibitors Scriptaid and LBH589 Combined with the Oncolytic Virus Delta24-RGD Exert Enhanced Anti-Tumor Efficacy in Patient-Derived Glioblastoma Cells

Lotte M.E. Berghauser Pont, Anne Klein, Jenneke J. Kloezman, Wouter van den Bossche, Johanna K. Kaufmann, Jeroen de Vrij, Sieger Leenstra, Clemens M.F. Dirven, Martine L.M. Lamfers

Published: May 18, 2015 | DOI: 10.1371/journal.pone.0127058
Viruses as Antitumor Weapons

\[
\begin{align*}
\frac{dx}{dt} &= rx \left(1 - \frac{x+y}{K}\right) - dx - \beta xy \\
\frac{dy}{dt} &= \beta xy + sy \left(1 - \frac{x+y}{K}\right) - ay - pyz \\
\frac{dz}{dt} &= cyz - bz
\end{align*}
\]

\[\text{(1)}\]

Wodarz, 2001

- \(x\) represents the uninfected tumor cells.
- \(y\) represents the infected tumor cells by virus.
- \(z\) represents the CTL cells.
Oncolytic Viral Model

\[
\frac{dx}{dt} = r x \left(1 - \frac{x + y}{K}\right) - \mu x - \beta x v \\
\frac{dy}{dt} = \beta x v + s y \left(1 - \frac{x + y}{K}\right) - \alpha y - \rho y z \\
\frac{dz}{dt} = \sigma y z - \phi z \\
\frac{dv}{dt} = N \alpha y - \xi v 
\]

- $x$ represents the Uninfected Tumor cells.
- $y$ represents the Infected Tumor cells by virus.
- $z$ represents the CD8 T cells.
- $v$ represents the Viral Load.
<table>
<thead>
<tr>
<th>Variable/Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$x$</td>
<td>Uninfected tumor cells</td>
</tr>
<tr>
<td>$y$</td>
<td>Infected tumor cells</td>
</tr>
<tr>
<td>$z$</td>
<td>CTL cells</td>
</tr>
<tr>
<td>$v$</td>
<td>Free virus population</td>
</tr>
<tr>
<td>$r$</td>
<td>Uninfected tumor cell growth rate</td>
</tr>
<tr>
<td>$\mu$</td>
<td>Uninfected tumor cell death rate</td>
</tr>
<tr>
<td>$\beta$</td>
<td>Viral infectious rate</td>
</tr>
<tr>
<td>$s$</td>
<td>Infected tumor cell growth rate</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>Lysing rate*</td>
</tr>
<tr>
<td>$K$</td>
<td>Tumor carrying capacity</td>
</tr>
<tr>
<td>$\rho$</td>
<td>Death from CTL cells</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>CTL response rate</td>
</tr>
<tr>
<td>$\phi$</td>
<td>CTL death rate</td>
</tr>
<tr>
<td>$\mathcal{N}$</td>
<td>Burst size of virions</td>
</tr>
<tr>
<td>$\xi$</td>
<td>viral decay rate</td>
</tr>
</tbody>
</table>

*rate of cytotoxic cell death and viral replication*
<table>
<thead>
<tr>
<th>Equilibrium State</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E_0(0, 0, 0, 0)$</td>
<td>Complete elimination of tumor.</td>
</tr>
<tr>
<td>$E_1\left(\frac{K(r-\mu)}{r}, 0, 0, 0\right)$</td>
<td>Failure of viral therapy.</td>
</tr>
<tr>
<td>$E_2\left(0, \frac{K(s-\alpha)}{s}, 0, \frac{NK\alpha(s-\alpha)}{s(\xi\kappa)}\right)$</td>
<td>Complete infection of tumor cells.</td>
</tr>
<tr>
<td>$E_3\left(0, \frac{b}{c}, \frac{\sigma K(s-\alpha) - s\phi}{\sigma\rho K}, \frac{\phi N\alpha}{\sigma(\xi)}\right)$</td>
<td>Complete viral prevalence in the tumor cell population in the presence of virus specific CTL response.</td>
</tr>
<tr>
<td>$E_4\left(x_4^<em>, y_4^</em>, 0, v_4^*\right)$</td>
<td>Coexistence of uninfected and infected tumor cells with suppressed immune system.</td>
</tr>
<tr>
<td>$E_5\left(x_5^<em>, y_5^</em>, z_5^<em>, v_5^</em>\right)$</td>
<td>Coexistence of uninfected and infected tumor cells with presence of CTL response.</td>
</tr>
</tbody>
</table>
Viral infection threshold

**Theorem**

Let \( r > \mu, s < \alpha \). Then the model has boundary equilibrium. The Viral Free Equilibria (VFE), \( E_1 = \left( \frac{K(r-\mu)}{r}, 0, 0, 0 \right) \), is L.A.S if
\[
\alpha - \frac{s \mu(\xi)}{r(\xi) - \beta KN(r-\mu)} > 0 \text{ whenever } \beta < \frac{r(\xi)}{NK(r-\mu)}.
\]

The Virus Free Equilibrium (VFE)

\[
\alpha > \frac{s \mu(\xi)}{r(\xi) - \beta KN(r-\mu)} \text{ when } \beta < \frac{r(\xi)}{KN(r-\mu)}.
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The Virus Free Equilibrium (VFE)

\[
\alpha > \frac{s\mu(\xi)}{r(\xi) - \beta KN(r-\mu)} \text{ when } \beta < \frac{r(\xi)}{KN(r-\mu)}.
\]

\[
R_0 = \frac{\beta N \alpha K(r-\mu)}{(\xi-\kappa)(\alpha r-\mu s)} < 1 \text{ when } \beta < \frac{r(\xi)}{NK(r-\mu)}.
\]

Let $V_0 = \frac{s\mu(\xi)}{r(\xi) - \beta KN(r-\mu)} \& \beta_c = \frac{r(\xi)}{KN(r-\mu)}$
Changes in VFE

\[ \alpha > V_0, \beta < \beta_c \]

\[ \beta = \beta_c \]

\begin{itemize}
  \item \text{Weak Lysing}
  \item \text{Intermediate Lysing}
  \item \text{Strong Lysing}
\end{itemize}

\begin{itemize}
  \item \text{Uninfected Cancer Cells}
  \item \text{Infected Cancer Cells}
  \item \text{Immune Response}
  \item \text{Virus}
\end{itemize}

\begin{itemize}
  \item \text{Overall tumor size, } x+y
  \item \text{Phase Plane}
\end{itemize}
\[ \beta > \beta_c \]

- **Populations**
  - Time scale (days)
  - Overall tumor size, \( x+y \)
  - \( \alpha = 0.01 \)
  - \( \alpha = 0.1 \)
  - \( \alpha = 0.5 \)
  - Weak Lysing
  - Intermediate Lysing
  - Strong Lysing

- **Phase Plane**
  - Uninfected
  - Infected
  - Phase Plane

- **Graphs**
  - Uninfected Cancer Cells
  - Infected Cancer Cells
  - Immune Response
  - Virus

- **Equations**
  - \( \beta > \beta_c \)
Complete Viral Prevalence

Theorem
Let $r < \mu, s > \alpha$. The model has complete viral prevalence at $E_2 = \left(0, \frac{K(s-\alpha)}{s}, 0, \frac{NK\alpha(s-\alpha)}{s(\xi)}\right)$. $E_2$ is L.A.S whenever $\sigma < \frac{\phi s}{K(s-\alpha)}$.

When $\sigma > \frac{\phi s}{K(s-\alpha)}$, the immune response rate is large enough to respond to the infected tumor cell population.
CTL response

\[ \sigma < \frac{\phi s}{K(s-\alpha)} \]

\[ \sigma > \frac{\phi s}{K(s-\alpha)} \]

![Graph showing populations and lyse rates over time](image1)

![Graph showing overall tumor size over time](image2)
Complete Viral Prevalence in the Presence of Immune Response

Theorem

Let \( s > \alpha, r < \mu, \sigma > \frac{\phi s}{K(s-\alpha)} \). The model has complete viral prevalence in the presence of CTL response at \( E_3 = (0, \frac{\phi}{\sigma}, \frac{\sigma K(s-\alpha)-s \phi}{\sigma \rho K}, \frac{\phi N \alpha}{\sigma(\xi)}) \). \( E_3 \) is an unstable saddle point whenever \( \sigma K[(\xi)(r - \mu)] - r \phi(\xi) - \beta KN \alpha \phi < 0 \).

\[
\frac{\sigma \beta NK \alpha \phi + r \phi(\xi)}{K(\xi)(r-\mu)} < 0
\]
Coexistence of Uninfected and Infected Populations in Presence of Immune Response

**Theorem**

Let \( s > \alpha, r > \mu, \sigma > S \). The equilibria of the coexistence of uninfected and infection cells in the presence of CTL cells is \( E_5 = (x_5^*, y_5^*, z_5^*, v_5^*) \). The model has an unstable point whenever

\[
\frac{\sigma \beta NK \alpha \phi + r \phi(\xi)}{K(\xi)(r - \mu)} > 0.
\]
CTL response

\[
\frac{\sigma \beta NK \alpha \phi + r \phi(\xi)}{K(\xi)(r-\mu)} < 0
\]

\[
\frac{\sigma \beta NK \alpha \phi + r \phi(\xi)}{K(\xi)(r-\mu)} > 0
\]
Theorem

Let $s < \alpha, r > \mu, \beta > \beta_1, \sigma > \frac{\beta NK\alpha b + rb(\xi)}{K(\xi)(r-\mu)}$. The equilibria of the coexistence of uninfected and infection cells in the absence of CTL cells is $E_4 = (x_4^*, y_4^*, 0, v_4^*)$. The model has an unstable point at $E_4$ whenever $\sigma < \frac{\phi s}{K(s-\alpha)}$. 

![Phase Plane](image_url)
Bifurcation at $E_4$
What are the viral-immune dynamics for oncolytic viruses?

How much time delay is needed from the immune response in order to allow for infection?

Is the immune system infected by virus?
Future Work

- Add immune response to cancer population
- Extend model to include a Hill function for immune response term
- Incorporate a delayed immune response on cancer-viral interactions
- Incorporate data for partial/full model
Acknowledgments

- Dr. Abba Gumel
- Dr. Ahmed Abdelrazec
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- Organizing committee: Drs. Urszula Ledzewicz, Avner Friedman & others
Thank you!

Dziękuję!