# Concerns Regarding the Efficacy of Utilizing the Vibrational Response of Aminocyanine Molecules to Near Infrared Light for Cancer Cell Destruction

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## ABSTRACT

Recent advancements in cancer treatment have introduced the use of aminocyanine molecules, activated by near-infrared (NIR) light, to induce vibrational responses that can selectively destroy cancer cells. This commentary critically examines a study that reports a 99% efficacy of this method against human melanoma cells in vitro, and significant tumor reduction in murine models. While the findings are promising, our analysis highlights crucial oversights in the study's implications for clinical applications. Specifically, the persistence of even a small fraction of cancer cells post-treatment poses significant risks for tumor regrowth and acquired resistance. Additionally, the study's approach neglects the heterogeneity of cancer cells and the presence of cancer stem cells, which are known to contribute to recurrence and resistance. We also discuss the limitations of the Tumor Control Probability (TCP) model in predicting treatment outcomes, emphasizing that achieving near-total eradication of cancer cells is necessary to prevent recurrence. Our commentary underscores the need for comprehensive research to address these challenges and ensure the efficacy and safety of novel cancer treatments utilizing aminocyanine molecules and NIR light.

## Keywords

Cancer; Near Infrared; Aminocyanine; Vibration; Antineoplastic Protocols; Radiotherapy

## Introduction

A recent paper in Nature Chemistry by researchers at Rice University reported that a new treatment method used by their team had a 99 percent efficiency against lab cultures of human melanoma cells, and half of the mice with melanoma tumors became cancer-free after treatment [1]. However, the report does not address the potential impact of the 1% remaining cells on regrowth, and it overlooks the role of cancer stem cells in the progression of the disease. This is akin to omitting a crucial piece of the puzzle while attempting to solve it. You might believe you've found the solution, but without the complete picture, you don't truly have the answer.

Their approach is based on a technique they refer to as 'using mechanical forces (jackhammers) at the molecular scale'. In this study,

aminocyanine molecules were employed as molecular vibrational agents. Aminocyanine molecules belong to a class of fluorescent synthetic dyes commonly used in medical imaging. These molecules can vibrate in synchronization when subjected to the appropriate stimulus, due to their structural and chemical properties. These vibrational modes exhibit a nearly symmetrical structure, with an arm on one side. Although the arm does not contribute to the vibrational motion, it aids in anchoring the molecule to the lipid bilayer of the cell membrane. The arm serves to stabilize the molecule, enhancing its interaction with the cell membrane. This interaction triggers a series of events leading to the internalization of the molecules by the cells. Once inside, these molecules can effectively destroy the cancer cells [2]. According to the study, this method displayed a 99 percent efficiency in combating laboratory cultures of human melanoma cells, and half of the mice with melanoma tumors achieved a cancer-free state following the treatment.

Even the presence of a single remaining tumor cell poses a significant challenge. These cells have the potential to multiply and form new tumors, complicating the treatment and cure of cancer. Furthermore, conventional cancer treatments may lose their effectiveness against these residual tumor cells due to a phenomenon referred to as acquired resistance [3].

In radiotherapy, a treatment protocol that kills all tumor cells except one cell may not result in an acceptable tumor control probability (TCP) due to several factors including:

**1. Tumor Cell Heterogeneity:** Tumor cells are not identical and may have different sensitivities to radiation therapy. Some cells may be more resistant to radiation and survive treatment, leading to a lower TCP [4].

**2. DNA Repair Mechanisms:** Cancer cells have various mechanisms to repair their DNA after radiation exposure, which can reduce the effectiveness of radiotherapy. DNA damage repair pathways encompass homologous recombination, base excision repair, and nucleotide excision repair [5]. These pathways play a crucial role in the survival of cancer cells, consequently leading to a lower TCP.

**3. Treatment Dose and Fractionation:** The dose of radiation and the number of fractions (sessions) given can impact the effectiveness of radiotherapy. Higher doses per fraction or fewer fractions may result in better tumor control, but this can also increase the risk of side effects [6].

**4. Margins of Error:** Radiation therapy is a precise treatment, but there can still be some margin of error in targeting the tumor [7]. This may lead to some cancer cells surviving the treatment.

**5. Tumor Size and Location:** The size and location of the tumor can affect the effectiveness of radiotherapy. Larger tumors or tumors in sensitive areas may be more challenging to treat effectively.

**6. Interaction with Other Treatments:** Radiotherapy can be used in combination with other treatments, such as chemotherapy or surgery. The interaction between these treatments may affect the overall effectiveness of radiotherapy [8].

Given this consideration, factors such as tumor cell heterogeneity, DNA repair mechanisms, treatment dose and fractionation, margins of error, tumor size and location, and interaction with other treatments determine the tumor control probability of any therapeutic scenario. TCP can further be affected by patient-related factors such as age, gender, and overall health [9]. These factors can have a significant impact on the outcome of any therapeutic treatment.

**7. The Tumor Control Probability (TCP) Model:** The Tumor Control Probability (TCP) is a model used to predict the likelihood that a radiotherapy treatment will completely eliminate all cancerous cells in a tumor. TCP is based on the idea that, given a certain population size, the number of events that occur

in a given period of time follows a Poisson distribution. The expected number of events is calculated by multiplying the population by the rate of occurrence [10]. The formula: $TCP = e^{-(M*SF)}$, where:

- TCP stands for Tumor Control Probability, which is the chance (expressed as a percentage) of successfully eradicating all cancer cells.
- e is the base of the natural logarithm, approximately equal to 2.71828.
- M is the number of surviving tumor cells after treatment.
- SF is the surviving fraction, which represents the proportion of cells that survive after a given dose of radiation.

The surviving fraction (SF) is a crucial concept in radiotherapy. It denotes the ratio of cells that survive after exposure to a specific dose of radiation. A high SF implies that more cells will survive after treatment, reducing the efficacy of the therapy. In a perfect scenario, SF would be 0, meaning no cells would survive treatment. However, due to various factors, such as radioresistance of the cancer cells and heterogeneity within the tumor, some cells may survive, resulting in an SF greater than 0. The lower the SF, the higher the chances of achieving a higher TCP.

The Poisson statistical model assumes that the probability of a given number of events happening in a fixed interval of time or space is independent of the time since the last event. For TCP, the "events" are the survival of cancer cells after radiation treatment. The Poisson model assumes that each cell's survival is an independent event and the number of cells that survive follows a Poisson distribution. This model provides an effective framework to investigate the effect of radiation on tumor cell populations.

When the treatment is such that all but one cell is killed, M (the number of surviving cells) is 1. If we assume that SF is 1 (meaning there's no further reduction in survival for the remaining cells), then the TCP would be $\approx 1/e$ or $1/2.71828 \approx 0.368$, or 36.8%.

In practice, a TCP of 100% is never achievable because there's always a chance, however small, that at least one cell might survive. The goal of radiotherapy is to reduce that chance to as low as possible by minimizing the SF.

## Conclusion

In summary, although the idea of eliminating 99% of cancer cells in a treatment method may initially seem promising, it proves to be insufficient when we consider the scale of the challenge. For instance, a tumor weighing 1-gram (1 cc), which is barely detectable, contains approximately a billion ($10^9$) cancer cells. Thus, even if we were to eliminate 99% of these cells, we would still be left with $10^7$ cancer cells, and most tumors tend to be larger than 1 cc. Therefore, if the claim of "99%" is to be taken literally, it could potentially present a problem. It is therefore necessary to conduct further research to ensure that the cancer does not recur following the implementation of any treatment that claims to eliminate nearly all cancer cells.

## Authors' Contribution

SMJ. Mortazavi, J. Welsh, and L. Sihver conceived the research idea. SMJ. Mortazavi and L. Sihver supervised the study. P. Faghani-Eskandarkolaei, SAR. Mortazavi and SMJ. Mortazavi drafted the manuscript. P. Faghani-Eskandarkolaei, J. Welsh and SAR. Mortazavi have equally contributed to this work. All authors contributed to the writing, critically reviewed the manuscript, and read and approved the final version.

## Conflict of Interest

L. Sihver, J. Welsh and SMJ. Mortazavi as the Editorial Board Members, were not involved in the peer-review and decision-making processes for this manuscript.

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