



# Localized Plasmonic Photothermal Therapy as a Life-saving Treatment Paradigm for Hospitalized COVID-19 Patients

Hagar I. Labouta<sup>1,2,3,4</sup> · Nasrin Hooshmand<sup>5</sup> · Tushar Upreti<sup>1</sup> · Mostafa A. El-Sayed<sup>5</sup>

Received: 18 August 2020 / Accepted: 4 December 2020 / Published online: 20 January 2021  
© The Author(s), under exclusive licence to Springer Science+Business Media, LLC part of Springer Nature 2021

## Abstract

Lung failure is the main reason for mortality in COVID-19 patients, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). To date, no drug has been clinically approved for treatment of COVID-19. Nanotechnology has a great potential in contributing significantly to the fight against COVID-19 by developing effective therapies that can selectively eradicate the respiratory virus load. We propose a novel COVID-19 management approach that is efficient in eliminating the virus load from the airways and protecting the lungs from the fatal effects of the virus. This approach relies on targeting the virus using ACE-2-functionalized gold nanorods (AuNRs) followed by irradiation with near-infrared (NIR) light for the selective eradication of SARS-CoV-2 without off-target effects, i.e., targeted plasmonic photothermal therapy. Using discrete dipole approximation (DDA), we quantitatively determined the efficiency of AuNRs (31 nm × 8 nm) in absorbing NIR when present at different orientations relative to one another on the surface of the virus. The safety and the local administration of AuNRs using a well-tolerated flexible bronchoscopy technique, commonly used for hospitalized COVID-19 patients, ensure feasibility and clinical translation. While requiring further research, we anticipate this approach to result in a first-line treatment for hospitalized COVID-19 patients that are experiencing severe respiratory conditions or belong to a high-risk population, e.g., seniors and diabetic patients.

**Keywords** COVID-19 · SARS-CoV-2 · Plasmonic photothermal therapy · Plasmonic coupling · Gold nanorods · Flexible bronchoscopy

---

Hagar I. Labouta and Nasrin Hooshmand equally contributed on this work.

- ✉ Hagar I. Labouta  
Hagar.Labouta@umanitoba.ca
- ✉ Nasrin Hooshmand  
nhooshmand3@gatech.edu
- ✉ Mostafa A. El-Sayed  
melsayed@gatech.edu

- <sup>1</sup> College of Pharmacy, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba, Canada
- <sup>2</sup> Children's Hospital Research Institute of Manitoba, Winnipeg, Manitoba, Canada
- <sup>3</sup> Biomedical Engineering, University of Manitoba, Winnipeg, Manitoba, Canada
- <sup>4</sup> Faculty of Pharmacy, University of Alexandria, Alexandria, Egypt
- <sup>5</sup> Laser Dynamics Laboratory, School of Chemistry and Biochemistry, Georgia Institute of Technology, Atlanta, GA, USA

## Introduction

Since the outbreak of the novel coronavirus disease, COVID-19 pandemic, caused by the SARS-CoV-2 virus, has spread rapidly around the globe. To date, there is no clinically approved treatment for COVID-19 with a solid evidence supporting its viability and reliability. While the RNA virus is rapidly mutating, it is crucial to think out-of-the-box for effective management approaches that can treat COVID-19 patients and save lives.

Photothermal therapy (PTT) has gained attention as a localized treatment paradigm suitable for the treatment of both cancer and bacterial infection. Photothermal agents convert near-infrared light (NIR) to moderate heating in a specific target region, termed hyperthermia, for tens of minutes to kill cancer cells or pathogens [1]. Recent advances in nanotechnology have significantly improved the efficiency of this technique by developing novel plasmonic nanomaterials with high photothermal conversion efficiency, biocompatibility, and ability to selectively target cancer

cells with minimal invasiveness to the normal cells. The localized surface plasmon resonance (LSPR) properties of plasmonic nanoparticles depend on several factors including the nanoparticle type, size, shape, inter-particle separation, and the dielectric function of the surrounding media [2–10]. Plasmonic nanoparticles made of silver [11], gold [12], and copper [13] have been widely used for photothermal treatment of bacterial infections. Selective binding to bacteria was made possible via surface functionalization of nanoparticles; this was followed by bacterial inactivation using PTT [12, 14–16]. For instance, surface functionalization of gold nanorods (AuNRs) with DNA aptamer allowed for selective targeting of methicillin-resistant *Staphylococcus aureus* (MRSA) followed by inactivation via PTT [16]. For our purpose, we propose to extend this conjugation technique of AuNRs to selectively apply plasmonic PTT for the inactivation of viruses, more specifically, SARS-CoV-2 virus.

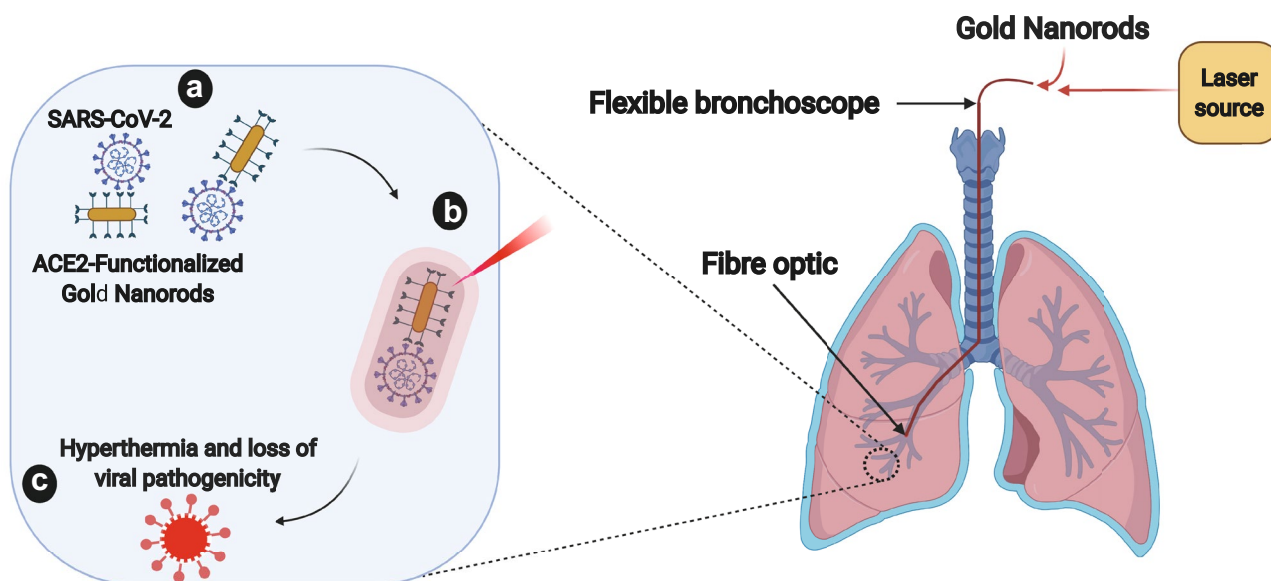
### Targeted Hyperthermia-based Eradication of SARS-CoV-2 Virus Load in the Airways of Infected Patients

Our proposed approach for the treatment of COVID-19 patients is based on the reported effectiveness of plasmonic photothermal therapy in targeting and killing pathogens [11–13], as well as the reported heat elimination of SARS-CoV-2 infectivity [17]. The feasibility of this

approach is justified by the ease of delivery of both gold nanoparticle dispersion and laser energy into the distal airways using flexible bronchoscopy, the most frequently performed invasive procedure in pulmonary medicine [18]. Flexible bronchoscopy is a well-tolerated procedure that is performed with relative ease in case of hospitalized COVID-19 patients. In addition to laser treatment locally, flexible bronchoscopy is a versatile approach that is used for several purposes such as collecting specimens from the lower respiratory tract, e.g., bronchoalveolar lavage for SARS-CoV-2, removing sputum or blood clots, injecting saline, epinephrine, vasopressin, and fibrin, as well as injecting medications such  $\alpha$ -interferon and N-acetylcysteine [19, 20]. Flexible bronchoscopy is also recommended as a safe and an effective diagnostic and therapeutic tool in pediatric care [21].

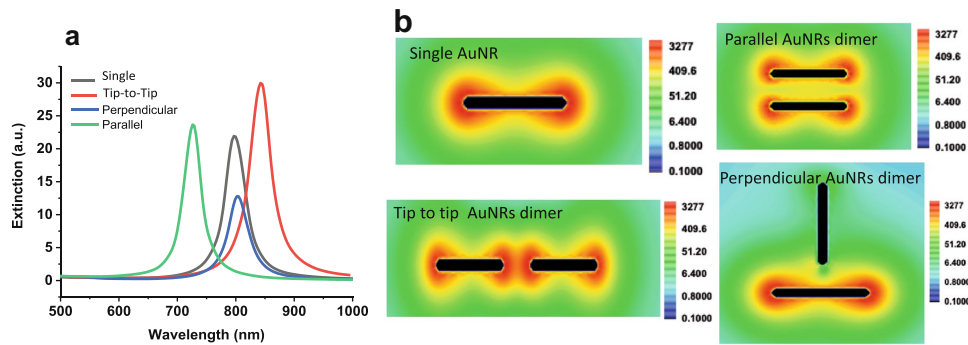
### Nanosystem Design

Gold nanoparticles are inert and biocompatible, and absorb light in the visible and NIR region of the electromagnetic spectrum [1, 22, 23]. Gold nanoparticles could be prepared in different shapes: nanospheres, nanorods, and nanoshells. Compared with nanospheres, AuNRs have a maximum LSPR absorbance in the NIR region, whereas nanospheres absorb strongly at the visible region [1, 24]. Knowing that NIR has a deeper tissue penetration than the visible light and a minimal absorption by these tissues, AuNRs are a



**Fig. 1** Novel approach for management of hospitalized COVID-19 patients. We are proposing plasmonic photothermal therapy as a safe and effective therapy using flexible bronchoscopy to introduce the AuNRs and apply NIR radiation locally in the distal airways. **a** Interaction of

AuNRs with SARS-CoV-2 is dictated by surface-functionalization with ACE-2. **b** Virus-bound AuNRs absorbs NIR light, **c** resulting in hyperthermia and loss of virus pathogenicity at elevated temperature



**Fig. 2 a** The extinction spectra of a single AuNR and dimers in three configurations, tip-to-tip, parallel, and perpendicular. The LSPR peak of parallel AuNRs is blue-shifted (shifted towards a shorter wavelength) and has slightly higher intensity of the plasmon band, relative to the plasmon peak of a single AuNR. On the other hand, the LSPR peak of the tip-to-tip AuNRs is red-shifted

(shifted towards a longer wavelength) and has the highest intensity of absorbed light. **b** Calculated spatial field distribution for single AuNR and the tip-to-tip, parallel, and perpendicular dimers of AuNRs. The wavelength of excitation was chosen based on the maximum peak for each extinction spectrum: 798 nm, 851 nm, 732 nm, and 798 nm, respectively

suitable candidate for use in plasmonic PTT [25]. AuNRs were also shown to have a significantly higher efficiency rate of converting photons into heat when compared with nanoshells, which also use NIR region laser for PTT [24, 26, 27]. Therefore, AuNRs will be the ideal nanoparticles for use in plasmonic photothermal elimination of SARS-CoV-2 viral load in the respiratory tract of infected patients.

The spike (S) protein of SARS-CoV-2 facilitates viral entry into target cells. SARS-CoV-2-S protein uses the receptor, angiotensin-converting enzyme 2 (ACE-2) for mediating binding with and entry into host cells. ACE-2 is a membrane-associated aminopeptidase which is highly expressed in human airway epithelia especially by alveolar type 2 cells of the lung, along with other tissues and organs [28]. We are proposing a novel therapeutic approach that employs the natural host cell receptor binding mechanism of the virus. In specific, functionalization of AuNRs with ACE-2 improves the selectivity of the nanorods to SARS-CoV-2 in the airways and minimize off-target accumulation (Fig. 1).

### Plasmonic Coupling and Photothermal Heat Generation

We examined the amount of light absorbed by protein ACE-2-functionalized AuNRs, which then is converted to heat energy and transferred onto the bound virus. However, the relative spatial orientation of AuNRs determines the amount and the wavelength of the absorbed light. Early reports by us and others indicate that plasmonic nanoparticles, when present a few nanometers apart from each other, resonant with the external field and the interaction between the nanoparticles is greatly enhanced due to plasmonic dipolar coupling [2, 10, 29–33]. This results in LSPR shifts in wavelengths, and change in LSPR spectral shape and field intensity.

Herein, we used the discrete dipole approximation (DDA) [29] as a powerful theoretical technique to model and calculate the optical properties of single AuNR and AuNR dimers (Supplementary information). The plasmonic interaction between the AuNRs were identified by the extent of the shift and the intensity of the plasmon band. We examined the field strength and extinction spectra for three possible configurations; tip-to-tip, parallel, and perpendicular dimers of AuNRs potentially present in a close proximity on the surface of the virus (i.e., SARS-COV-2). The results of these simulation experiments are summarized in Figs 2 and S1.

Figure 2a shows the extinction spectra as a function of the wavelength for a single AuNR and a dimer of AuNRs in tip-to-tip, parallel, and perpendicular configuration with inter-particle separation of 10 nm, the maximum distance beyond which the plasmonic interaction between these examined rods decays. Single AuNRs were shown to efficiently absorb most of the incident light at the resonance wavelength, 798 nm, with minimal proportion of the radiation being scattered (Fig. S1). On exciting an individual dimer of AuNRs with a tip-to-tip configuration with an incident light linearly polarized along the dimer axis at the resonance wavelength, the interaction between the AuNRs exhibits a resonance peak at 851 nm. For the parallel and perpendicular AuNR dimer, the LSPR wavelengths were observed at 732 nm and 798 nm, respectively.

The formation of a strong field (hot spots) between the nanorods can offer additional source of heat at the surface of the virus. This was calculated by solving the appropriate Maxwell's equations (Fig. 2b) [34]. In the tip-to-tip AuNR dimer, the oscillating dipoles extracted from the facing tips were shown to have a strong effect on the LSPR coupling of AuNRs resulting in hot spots formed between the two nanorods. This is due to the strong plasmonic coupling between the two facing tips in the tip-to-tip AuNR dimer resulting in a higher intensity

of absorbed light, as compared with other potential configurations (Fig. 2). This suggests that for the tip-to-tip dimer, the increased electron density generated at the tip of each nanorod results in a stronger field at the region in-between the two nanorods. Within the biological environment, this narrow gap can occur in case of nanorod aggregates, resulting in highly localized photothermal heat generation that has a significant influence on the bound virus viability and the increase in the total photothermal temperature can drive the deformation of the bound virus.

In summary, our results demonstrate that the field and the extinction intensities are highly tunable and sensitive to the assembly structures. The NIR light is efficiently absorbed by single AuNRs. Among the different possible orientations of the aggregated AuNRs, the field intensity is stronger in the case of tip-to-tip orientation due to the strong hot spot generated between the two nanorods. This optical property and the subsequent heat generation of AuNRs will result in elevated temperatures (in the order of few tens of degrees) of the species (i.e., virus) bound to the surface of AuNRs or localized in their vicinity (gap region) [35]. In this regard, the tip-to-tip orientation is the best potential configuration with a high efficiency of inducing hyperthermia.

### Immune Recognition of AuNRs

Another point of consideration is the potential recognition and uptake of AuNRs by the immune cells, e.g., macrophages at the distal airways [36]. Due to the ability of macrophages to internalize gold nanoparticles, there is a risk of hyperthermia in these host cells and toxicity when photothermal therapy is used to eradicate viruses in the lung [37]. This could be avoided by tailoring the characteristics of AuNRs to minimize off-target accumulation. For instance, uptake of gold nanorods by macrophages is size-dependent [38]. Therefore, optimizing the size of AuNRs will reduce accumulation inside the macrophage and, hence, minimize unwanted effects. Alternatively, the functionalization of nanoparticles with polyethylene glycol (PEG) is a common technique to reduce opsonization and thereby reduce nanoparticle recognition by immune cells [39]. Because of the immune-modulating effects of PEG surface coatings, particles coated with PEG are often referred to as “stealth” particles [40, 41].

### Elimination of AuNRs from the Respiratory Tract

After developing a selective plasmonic PTT for the elimination of SARS-CoV-2 virus from the respiratory tract, the safety and the clearance of AuNRs must also be considered. Nanoparticles are known to be able to translocate through the alveolar epithelium into the systemic circulation, and this translocation has been shown to be inversely proportional to the size of gold nanoparticles, but, independent from the

nanoparticle concentration [42]. Upon entering the systemic circulation, most of the AuNRs have been found to localize themselves in the macrophages in liver and spleen [43]. Therefore, size optimization of AuNRs can allow us to regulate the post-therapy elimination rate.

## Impact on the Global Response to the COVID-19 Pandemic

Given the absence of efficient therapies for COVID-19, we propose a novel approach to respond to the current need to address the significant stress that this pandemic places on the healthcare systems [44]. Taking advantage of the plasmonic photothermal properties of AuNRs, we project that research in this direction will result in a safe and an efficient therapy for hospitalized COVID-19 patients. This could be life-saving to high-risk populations, e.g., seniors and diabetics. This clinical approach has a high potential of translation to fast-track clinical trials based on a well-tolerated flexible bronchoscopy procedure that is performed with a relative ease for hospitalized COVID-19 patients, the approved efficiency of plasmonic photothermal therapy for pathogen targeting and eradication, and the established safety of gold nanoparticles.

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s11468-020-01353-x>.

**Acknowledgments** This work received financial support from NSF-CHE grant (1904351). This work was also supported by the Natural Sciences and Engineering Research Council (NSERC Discovery Grant-RGPIN-2020-05679) and University of Manitoba. T. Upreti was supported by Undergraduate Summer Research Award from the College of Pharmacy, University of Manitoba. N. Hooshmand and M. El-Sayed would like to acknowledge the Georgia Institute of Technology for providing high-performance computing resources and support. N. Hooshmand thanks B. T. Draine and P. J. Flatau for use of their DDA Code DDSCAT 6.1.

## References

- Huang X, Jain PK, El-Sayed IH, El-Sayed MA (2007) *Lasers Med Sci* 23:217–228
- Kelly KL, Coronado E, Zhao LL, Schatz GC (2002) *J Phys Chem B* 107:668–677
- Lee K-S, El-Sayed MA (2006) *J Phys Chem B* 110:19220–19225
- Liz-Marzán LM (2005) *Langmuir* 22:32–41
- Sherry LJ, Chang S-H, Schatz GC, Van Duyne RP, Wiley BJ, Xia Y (2005) *Nano Lett* 5:2034–2038
- Link S, Wang ZL, El-Sayed MA (1999) *J Phys Chem B* 103:3529–3533
- Jensen TR, Malinsky MD, Haynes CL, Van Duyne RP (2000) *J Phys Chem B* 104:10549–10556
- Haynes CL, Van Duyne RP (2001) *J Phys Chem B* 105:5599–5611
- Murray WA, Auguie B, Barnes WL (2009) *J Phys Chem C* 113:5120–5125

10. Hooshmand N, Bordley JA, El-Sayed MA (2014) *J Phys Chem Lett* 5:2229–2234
11. Hu B, Wang N, Han L, Chen M-L, Wang J-H (2015) *Acta Biomater* 11:511–519
12. Ngo-Duc T-T, Alibay Z, Plank JM, Cheeney JE, Haberer ED (2020) *ACS Appl Mater Interfaces* 12:126–134
13. Zhao Y, Cai Q, Qi W, Jia Y, Xiong T, Fan Z, Liu S, Yang J, Li N, Chang B (2018) *Chemi Sel* 3:9510–9516
14. Turek D, Van Simaey D, Johnson J, Ocsoy I, Tan W (2013) *World J Transl Med* 2:67–74
15. Wang J, Gao J, Liu D, Han D, Wang Z (2012) *Nanoscale* 4:451–454
16. Ocsoy I, Yusufbeyoglu S, Yılmaz V, McLamore ES, Ildiz N, Ülgen A (2017) *Colloids Surf B: Biointerfaces* 159:16–22
17. Duan SM, Zhao XS, Wen RF, Huang JJ, Pi GH, Zhang SX, Han J, Bi SL, Ruan L, Dong XP (2003) *Biomed Environ Sci* 16:246–255
18. Wang K-P, Mehta AC, Turner JF (2012) *Flexible bronchoscopy*. West Sussex: Wiley-Blackwell
19. Liang T. (2020) *Handbook of COVID-19 Prevention and Treatment. the first Affiliated Hospital. Zhejiang University School of Medicine. Compiled according to clinical experience*
20. Force T (2020) *Sci Insigt* 33:138–158
21. Davidson MG, Coutts J, Bell G (2008) *Pediatr Pulmonol* 43:1188–1192
22. Murphy CJ, Gole AM, Stone JW, Sisco PN, Alkilany AM, Goldsmith EC, Baxter SC (2008) *Acc Chem Res* 41:1721–1730
23. Labouta HI, Schneider M (2010) *Int J Pharm* 395:236–242
24. Huang X, El-Sayed IH, Qian W, El-Sayed MA (2006) *J Am Chem Soc* 128:2115–2120
25. Weissleder R (2001) *Nat Biotechnol* 19: 316–317
26. Kim HS, Lee DY (2018) *Polym* 10:961
27. Hirsch LR, Stafford RJ, Bankson JA, Sershen SR, Rivera B, Price RE, Hazle JD, Halas NJ, West JL (2003) *PNAS* 100:13549–13554
28. Hoffmann M, Kleine-Weber H, Krüger N, Müller M, Drosten C, Pöhlmann S (2020) *bioRxiv* 2020.2001.2031.929042
29. Draine BT, Flatau PJ (1994) *J Opt Soc Am A* 11:1491–1499
30. Jain PK, Lee KS, El-Sayed IH, El-Sayed MA (2006) *J Phys Chem B* 110:7238–7248
31. Hooshmand N, Bordley JA, El-Sayed MA (2016) *J Phys Chem C* 120:4564–4570
32. Hooshmand N, El-Sayed MA (2019) *Proc Natl Acad Sci* 116:19299–19304
33. Bordley JA, Hooshmand N, El-Sayed MA (2015) *Nano Lett* 15:3391–3397
34. Mie G (1908) *Ann Phys* 25:377–445
35. Link S, El-Sayed MA (2000) *Int Rev Phys Chem* 19:409–453
36. Lingabathula H, Yellu N (2017) *Environ Toxicol Pharmacol* 52:248–254
37. Thorley AJ, Ruenaroengsak P, Potter TE, Tetley TD (2014) *ACS Nano* 8:11778–11789
38. Li Z, Huang H, Tang S, Li Y, Yu X-F, Wang H, Li P, Sun Z, Zhang H, Liu C, Chu PK (2015) *Biomaterials* 74:144–154
39. Chaudhari KR, Ukawala M, Manjappa AS, Kumar A, Mundada PK, Mishra AK, Mathur R, Monkkonen J, Murthy RS (2012) *Pharm. Res.* 29:53–68
40. Li SD, Huang L (2010) *J Control Release* 145:178–181
41. Labouta HI, Gomez-Garcia MJ, Sarsons CD, Nguyen T, Kennard J, Ngo W, Terefe K, Iragorri N, Lai P, Rinker KD, Cramb DT (2018) *RSC Adv* 8:7697–7708
42. Bachler G, Losert S, Umehara Y, von Goetz N, Rodriguez-Lorenzo L, Petri-Fink A, Rothen-Rutishauser B, Hungerbuehler K (2015) *Part Fibre Toxicol* 12:18
43. Tong L, He W, Zhang Y, Zheng W, Cheng J-X (2009) *Langmuir* 25:12454–12459
44. Chan WCW (2020) *ACS Nano* 14: 3719–3720

**Publisher's Note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.