Targeted Delivery of Therapeutic Cargo Using Synthetically Modified MS2 Viral Capsids

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Viral capsids offer many exciting opportunities as new platforms for the tissue-specific delivery of therapeutic cargo. Through appropriate surface modification, multiple copies of a desired targeting group can be displayed to direct these carriers to cell surface markers of interest. The use of hollow structures allows drug molecules and radiolabels to be sequestered within the assemblies, protecting them from premature degradation and masking their influence on biodistribution.

To realize this potential, we have developed a series of site-selective chemical reactions to convert the protein shell of bacteriophage MS2 into a coordinated set of targeted delivery agents. Through the use of tyrosine and cysteine coupling chemistry we have developed efficient methods to install 100-180 copies of high-relaxivity MRI contrast agents,[1] cryptophane cages for the binding of hyperpolarized xenon atoms,[2] F-18 labels for PET imaging,[3] taxol for tumor treatment,[4] and porphyrins for use in photodynamic therapy.[5] We have also developed a new bioorthogonal coupling reaction that can modify *p*-aminophenylalanine, an artificial amino acid introduced using amber stop codon suppression technique.[6] This has allowed the installation of peptides,[7] DNA aptamers,[8] and even full-sized proteins on the external surface of the capsids, giving them the ability to bind to a number of different tumor cell lines with high affinity and selectivity.

This presentation will detail the synthetic methods that have been developed for the synthesis of these multivalent nanoscale delivery vehicles, and will describe their ability to direct imaging agents and drug molecules to specific cancer targets.

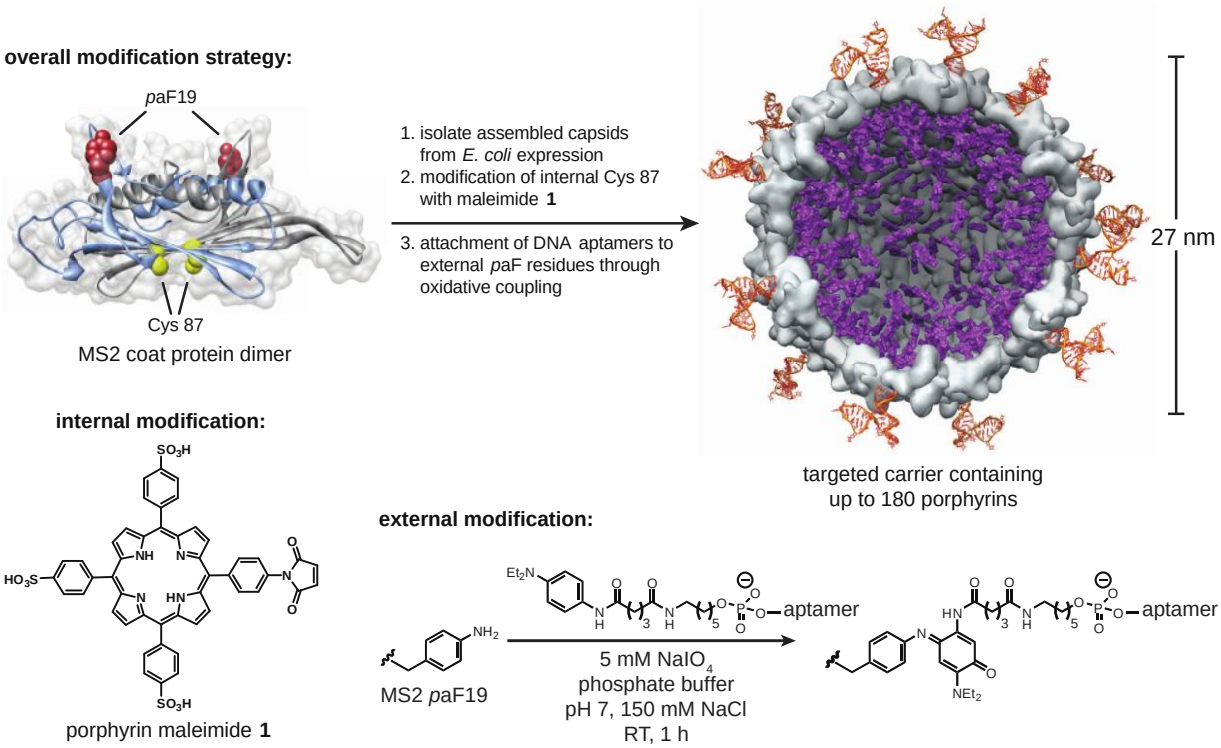

Figure 1. Synthesis of a viral capsid based agent for targeted photodynamic therapy. 180 copies of a synthetic porphyrin were installed inside each genome-free MS2 viral capsid, giving them the ability to produce singlet oxygen upon illumination with 420 nm light. To endow the carriers with selective targeting capabilities, 20 copies of a tyrosine kinase 7 (PTK7) targeting aptamer were attached to the external surface through the modification of an artificial amino acid. The resulting structures were able to generate 300,000 equivalents of singlet oxygen in 20 min, leading to the selective and efficient destruction of PTK7 positive Jurkat leukemia cells.

References

1. Hooker, J. M. ; Datta, A.; Botta, M.; Raymond, K. N.; Francis, M. B. *Nano Letters* **2007***, 7, 2207-2210.*
2. Meldrum, T.; Seim, K. L.; Bajaj, V. S.; Palaniappan, K.; Wu, W.; Francis, M. B.; Wemmer, D. E.; Pines, A. *J. Am. Chem. Soc.* **2010***, 132*, 5936-5937.
3. Hooker, J. M.; O'Neil, J. P.; Romanini, D. W.; Taylor, S. E.; Francis, M. B. *Molecular Imaging in Biology* **2008**, 1536-1632.
4. Wu, W.; Hsiao, S. C.; Carrico, Z. M.; Francis, M. B. *Angewandte Chemie Int. Ed.* **2009**, *48*, 9493 - 9497*.*
5. Stephanopoulos, N.; Tong, G. J.; Hsiao, S. C.; Francis, M. B. *ACS Nano* **2010**, *4*, 6014-6020.
6. Mehl, R. A.; Anderson, J. C.; Santoro, S. W.; Wang, L.; Martin, A. B.; King, D. S.; Horn, D. M.; Schultz, P. G. *J. Am. Chem. Soc.* **2003**, *125*, 935–939.
7. Carrico, Z. M.; Romanini, D. W.; Mehl, R. A.; Francis, M. B. *Chemical Communications* **2008**, 1205-1207.
8. Tong, G. J.; Hsiao, S. C.; Carrico, Z. M. *J. Am. Chem. Soc.* **2009**, *131*, 11174–11178.