Supporting information for

Nucleic Acid-Metal Organic Framework (MOF) Nanoparticle Conjugates

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Section S1: Materials and general procedures

All reagents unless otherwise stated were obtained from commercial sources (Alfa Aesar, Cambridge isotope laboratories, Sigma Aldrich, Glen Research, Spec Certi Corp) and were used without further purification. Ultrapure deionized water (18.2MΩ resistivity) from a Millipore system was used. Yields reported were unoptimized.

Section S2: Synthesis of oligonucleotides

Oligonucleotides were synthesized using a Mermaid MM48 DNA synthesizer (Bio Automation) on a standard CPG solid phase support. All oligonucleotides were deprotected under conditions recommended by the manufacturer and purified by reverse-phase high performance liquid chromatography (HPLC). Characterization and determination of concentration was determined by matrix assisted laser desorption ionization (MALDI-TOF) mass spectrometry and UV-Vis, respectively. A complete list of oligonucleotides synthesized can be found in Table S1. Alkyl disulfide oligonucleotides were cleaved prior to use utilizing 100 mM dithiothreitol to yield the reduced alkylthiol oligonucleotides under standard conditions.[1]

Table S1: Oligonucleotides synthesized

3'TTT-TTT-TTT-T(T-Tamra)T -TTT -TTT -TTT -DBCO5'
3'TTT-TTT-TTT-TTT-TTT-TTT-TT-(T-DBCO)5'
3'TTT-TTT-TTT-T(T-fluorescein) T-TTT-TTT-TTT-DBCO5'
3'TTT-TTT-TTT-TTT-TTT-TTT-TTT-DBCO5'
3'TTA-TAA-CTA-TTC-CTA-AAA-AA-DBCO5'
3'TAG-GAA-TAG-TTA-TAA-AAA-AA-SH5'
3'TTT-TTT-TTT-TTT-TTT-TTT-TTT-SH5'

Section S3: Synthetic procedure for UiO-66-N_3 nanoparticles.

Caution: azides are an explosive hazard. Proceed with caution.

Ligand Synthesis

Synthesis of 2-Azido-1,4-benzenedicarboxylic acid was carried out under conditions reported by Kim *et al*.[2]

MOF nanoparticle synthesis

Synthesis of 14 nm UiO-66-N_3 ($Zr_6O_4OH_4(C_8H_3O_4\text{-}N_3)_6$

2-Azido-1,4-benzenedicarboxylic acid (50 mg, 0.24 mmol) was dissolved in 1 mL of *N,N* Dimethylformamide (DMF). In a separate vial, zirconyl chloride octahydrate (21 mg, 0.066 mmol) was dissolved in 3 mL of DMF. The two solutions were mixed together in a 10 mL scintillation vial, and acetic acid (300 µl) was added to the reaction mixture. The solution was heated at 90 ˚C for 18 h to yield UiO-66-N_3 ($Zr_6O_4OH_4(C_8H_3O_4\text{-}N_3)_6$. MOF nanoparticles were purified by centrifugation (15000 rpm, 90 min) followed by solvent exchange (3 x DMF and 3 x NANOpure H_2O) over a 48 h period. MOF nanoparticles were suspended in H_2O for characterization and functionalization with DNA.

Synthesis of 19 nm and 540 nm UiO-66-N_3($Zr_6O_4OH_4(C_8H_3O_4\text{-}N_3)_6$

Synthetic conditions as above were used, except the volume of acetic acid was changed to 400 µl and 3.5 mL for UiO-66-N_3-19 and UiO-66-540 nm, respectively.

Section S4: Synthesis of Nucleic Acid-(MOF) Nanoparticle Conjugates

Synthesis of 14 nm Nucleic acid Acid-MOF nanoparticle conjugates

UiO-66-N_3 MOF 14 nm nanoparticles (0.15 nmol in 0.5 mL) were added to an aqueous solution of DNA (25 nmol in 0.5 mL) and were mixed on a mechanical shaker

for 72 h at 40 ˚C. NaCl was added to the solution over six hours in three equal aliquots to a final concentration of 0.5 M. Free oligonucleotides were removed by centrifugation (3 x 15000 rpm for 90 minutes), followed by re-suspension of the nanoparticle oligonucleotide conjugates in H_2O for characterization and analysis.

Synthesis of 19 nm and 540 nm Nucleic acid Acid-MOF nanoparticle conjugates

Synthetic conditions as above were used, except the amount of nanoparticles were decreased from 0.15 nmol for 14 nm to 0.08 nmol and 8 x 10^{-7} nmol for 19 nm and 540 nm particles, respectively.

Section S5: Powder X-ray diffraction (PXRD)

Powder X-ray diffraction data (PXRD) were collected at Argonne National Laboratory utilizing the DOW-Northwestern-Dupont Collaborative Access team (DND-CAT) Beamline 5-ID-D at the Advanced Photon Light Source (APS). A wavelength of 1.239 Å was used for the data collection with an exposure time of 1 sec. Two-dimensional scattering data were converted to 1D data by taking a radial average of the 2D data. Prior to data collection, as-synthesized MOF nanoparticles were dried by filtration and washed with acetone. Samples for PXRD were placed in quartz capillaries (Charles Supper Company) (1.5 mm) for data collection. MOF-DNA conjugates were dispersed in solution following centrifugation and placed in quartz capillaries for data collection. The large solvent background in these samples is attributed to the dispersed nature of the samples.

The model for UiO-66-N_3 was generated in materials studio software with the crystal building software, utilizing cell parameters and atomic positions from UiO-66.[3-4] A Pawley refinement of PXRD data for the as-synthesized 540 nm nanoparticle MOF was used to optimize the unit cell parameter of UiO-66-N_3 (Figure S1).

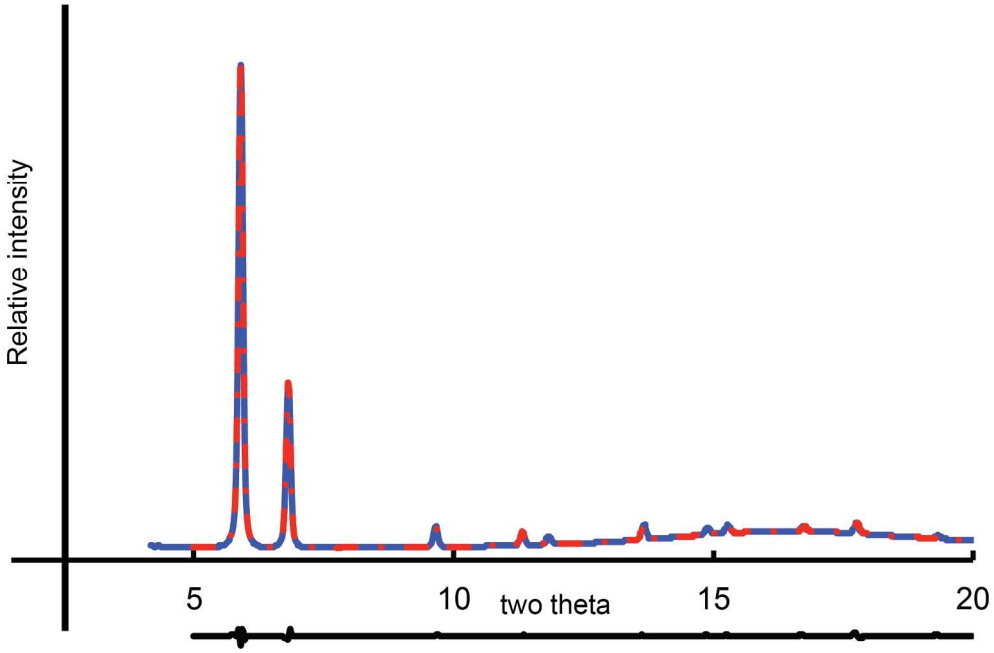

Figure S1: Pawley refinement of UiO-66-N_3-540 nm. Blue = experimental data, Red = fit, and black = difference.

Table S2: Final statistics from Pawley refinement.

Name	UiO-66-N_3
Crystal System	Cubic
Space group	9052.49(2)
α (Å)	20.8412(8)
R_p(%)	1.04
R_{wp}(%)	1.79
R_{wp}(%) - without background	3.93

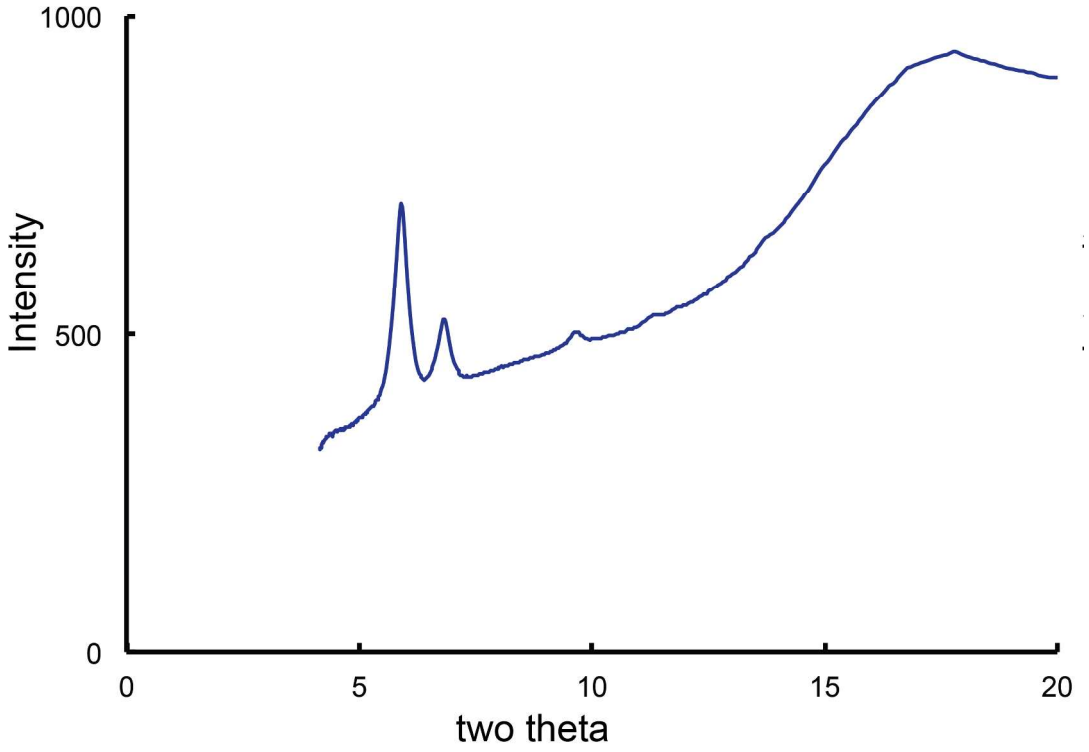

Figure S2: PXRD of 19 nm MOF-DNA conjugates suspended in H_2O.

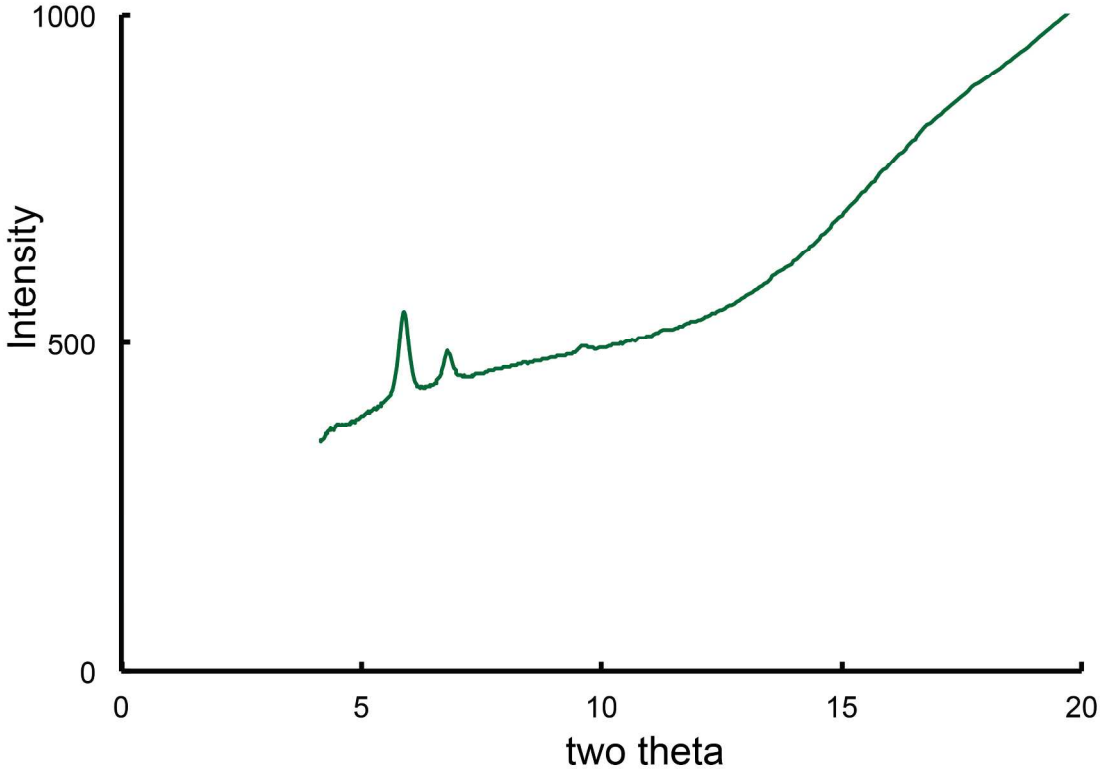

Figure S3: PXRD of 14 nm MOF-DNA conjugates suspended in H_2O.

Section S6: Inductively coupled plasma mass spectrometry (ICP-MS)

The zirconium contents of the as-synthesized MOF samples after solvent exchange (3 x DMF, 3 x H_2O) and MOF-DNA constructs after solvent exchange (3 x H_2O) were determined by inductively coupled plasma mass spectrometry (ICP-MS). ICP-MS analysis was carried out on a Thermo X series II ICP-MS instrument with an automated sample changer. MOF samples were dispersed homogenously in H_2O (1 mL), and 10 µl of the MOF sample was added to HNO_3 (990 µl). The samples were heated at 60 ˚C for 15 h to fully digest the MOF. Unknown samples were prepared with an internal multi-element standard and compared to a standard curve generated using a zirconium standard. In determining particle concentration, a unit cell size of 20.84 Å and a unit cell composition of $C_{192}H_{72}Zr_{24}O_{128}N_{72}$ were used.

Section S7: Transmission Electron microscopy and scanning electron microscopy

MOF nanoparticles were analyzed using a Hitachi HD-2300 scanning transmission electron microscope in either SE or TE modes with an accelerating voltage of 200 kV. Samples were dispersed onto TEM grids by drop-casting a dilute solution containing MOF crystals or MOF-DNA conjugates directly onto TEM grids. The average crystal size for each synthesis was determined by measuring the edge length of greater than fifty crystals from multiple syntheses under analogous synthetic conditions (**Figure S7**).

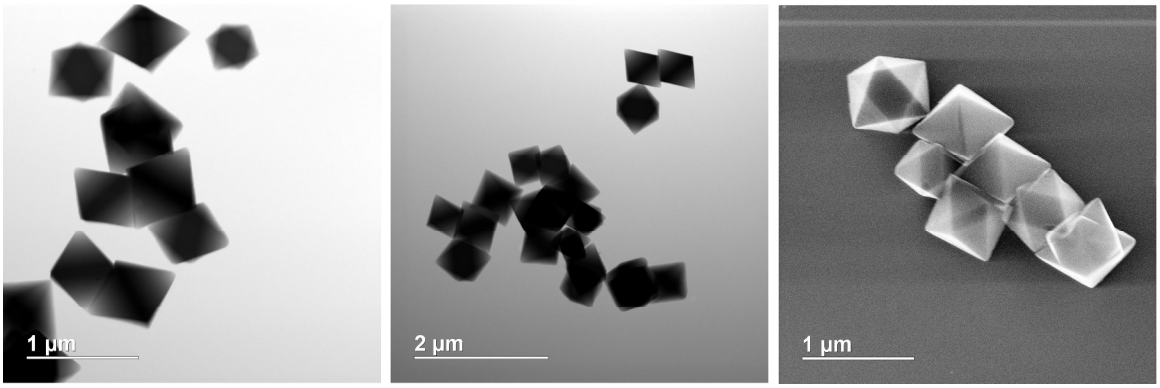

Figure S4: Representative transmission electron microscopy and scanning electron microscopy images of 540 nm nanoparticles.

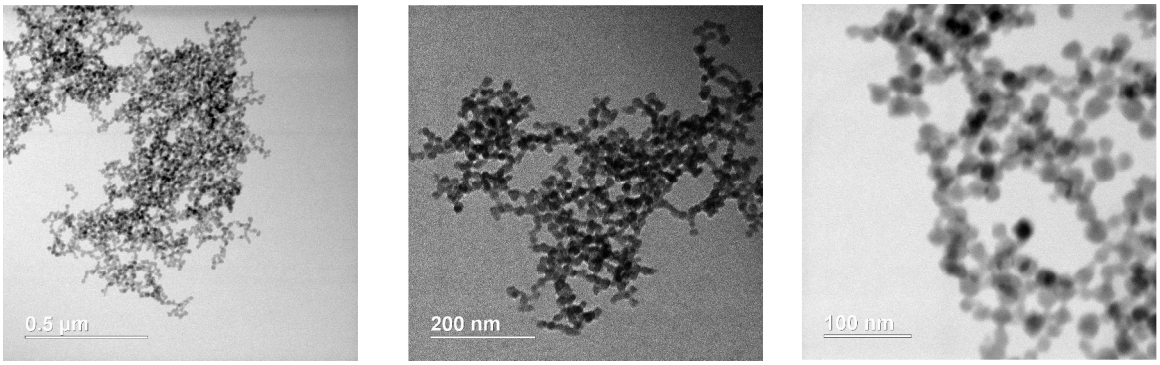

Figure S5: Representative transmission electron microscopy images of 14 nm nanoparticles.

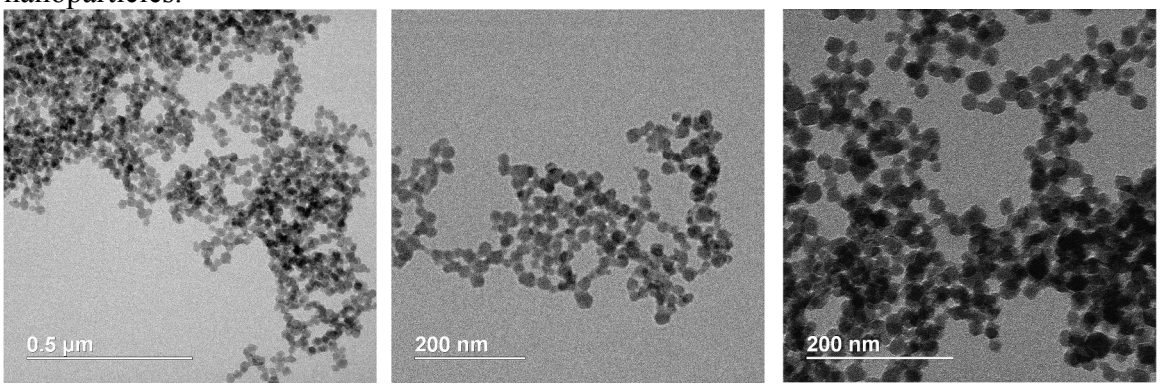

Figure S6: Representative transmission electron microscopy images of 19 nm nanoparticles.

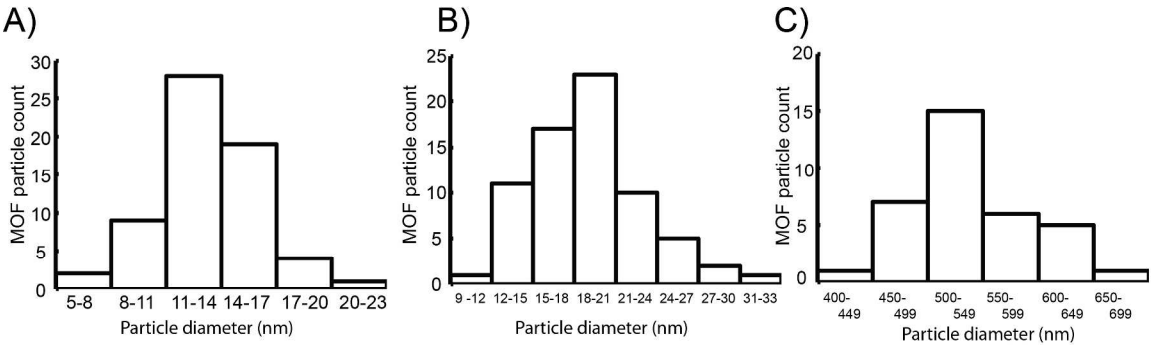

Figure S7: Nanoparticle size distributions for: A) 14nm, B) 19nm, and C) 540 nm MOF nanoparticles.

Section S8: Dynamic light Scattering (DLS) and zeta potential measurements.

Zeta potential and dynamic light scattering measurements of hydrodynamic radii were made on a Malvern Zetasizer Nano-ZS (Malvern Instruments). Results were averaged over ten measurements.

Section S9: Ultraviolet-visible (UV-Vis) absorbance

UV-Vis spectroscopy was performed on a Cary 5000 (Agilent) UV-Vis spectrometer fitted with a temperature stage. 1 cm quartz optical cells were utilized to make measurements. The surface coverages of DNA on the MOF nanoparticle-DNA conjugates were determined by UV-Vis, utilizing a dye labeled DNA sequence (3'TTT-TTT-TTT-T(T-Tamra)T -TTT -TTT –TTT -DBCO5').

UV-Vis absorbance of non-digested MOF nanoparticle-DNA conjugates

Concentrations of fluorophore-labeled DNA were determined by diluting purified nucleic acid-MOF nanoparticle conjugates in NANOpure H_2O. Serial dilution showed a linear relationship between absorbance and concentration at 556 nm (Figure S8).

UV-Vis absorbance of digested MOF nanoparticle-DNA conjugates

Concentrations of fluorophore-labeled DNA were determined by digestion of nucleic acid-MOF nanoparticle conjugates in 0.1 M NaOH for 18 h under mechanical shaking. Studies of free DNA showed no significant decrease (≈ 4%) in fluorophore absorbance in 0.1 M NaOH after 18 h (Figure S9).

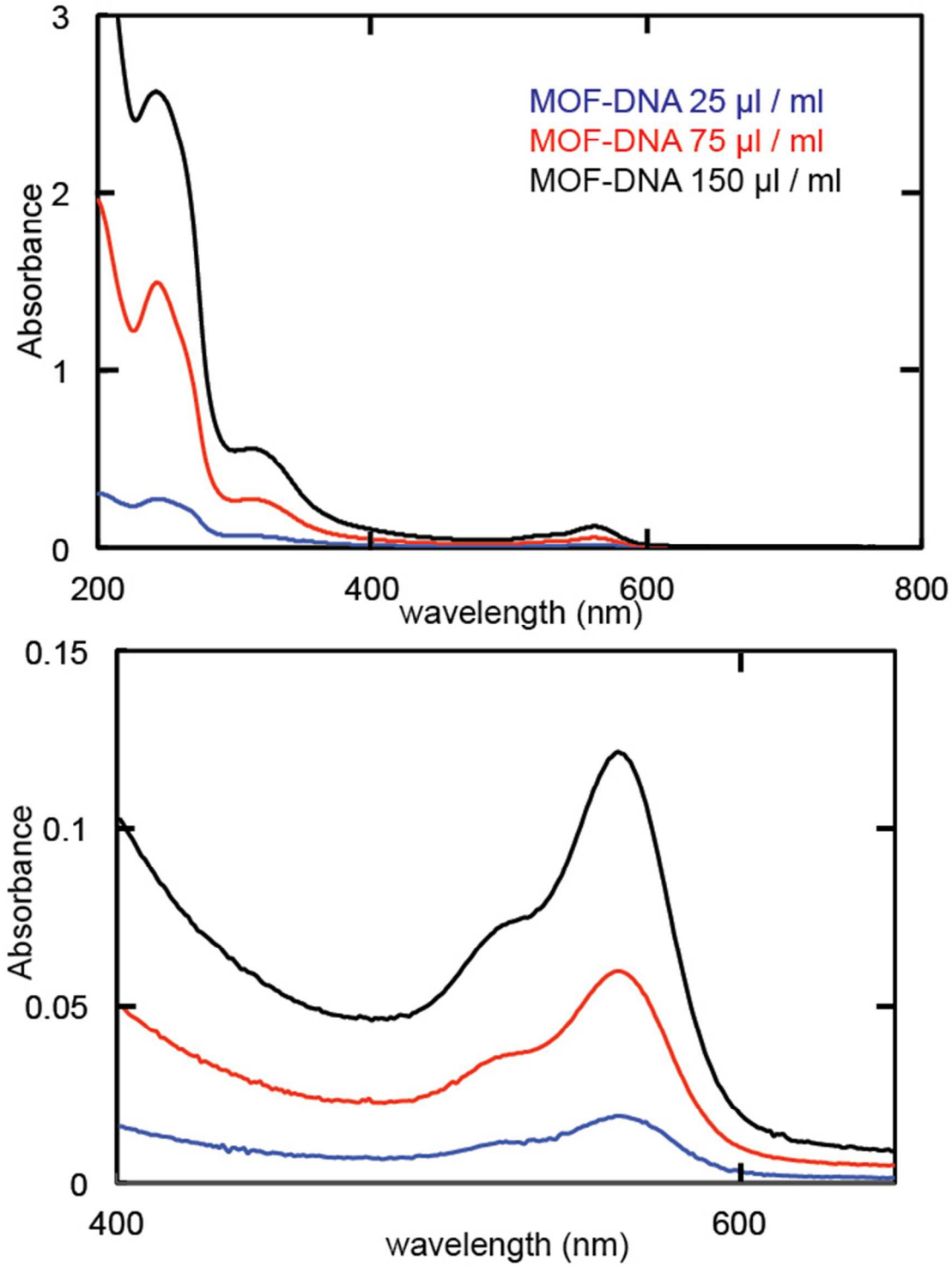

Figure S8: Absorption spectra of 14 nm nucleic acid-MOF nanoparticle conjugates at different concentration dispersed in water.

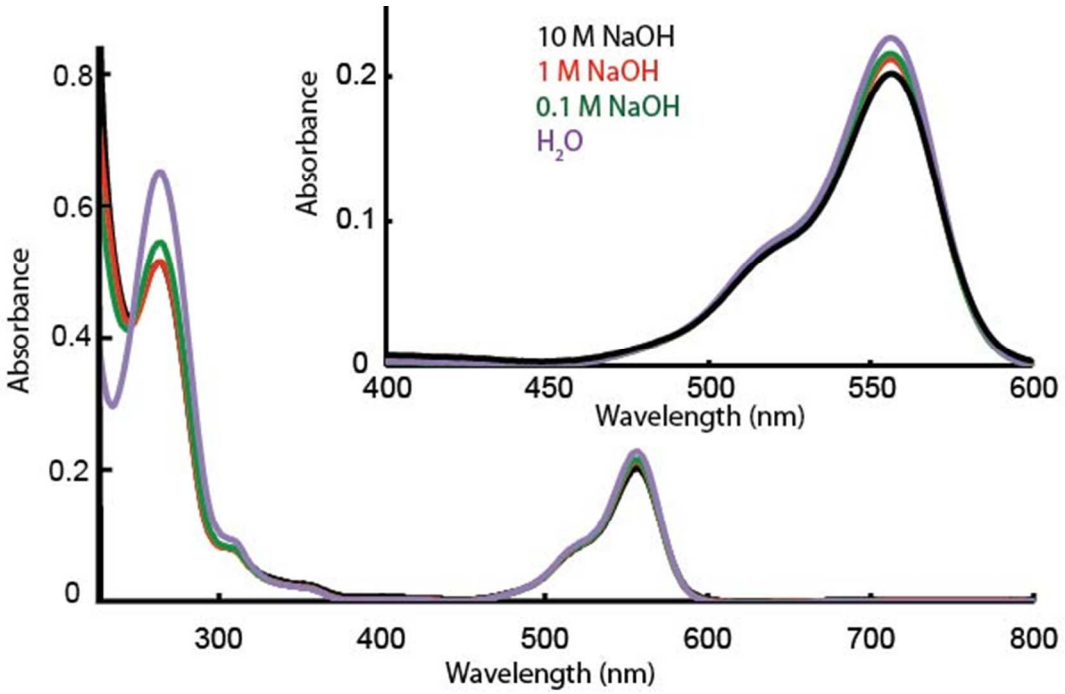

Figure S9: Absorbance spectra of fluorophore labeled DNA at different concentrations of NaOH.

Melting analysis

Au nanoparticles were functionalized with DNA utilizing previously reported conditions.[1] Melting analysis was performed for a binary assembly of MOF nanoparticle-DNA conjugates and gold nanoparticles by combining equal concentrations of each nanoparticle, followed by salting to 0.25 M NaCl and addition of 0.05% tween 20. Aggregation between particles containing complementary DNA was immediately observed upon the addition of NaCl. A melting analysis was carried-out by ramping the temperature at 0.25 ˚C/min from 25˚C to 85 ˚C. The extinction of the particles was monitored at 520 nm (the plasmon resonance for the dispersed gold particles). A melting transition was not observed for particles functionalized with non-complementary DNA (Figure S10).

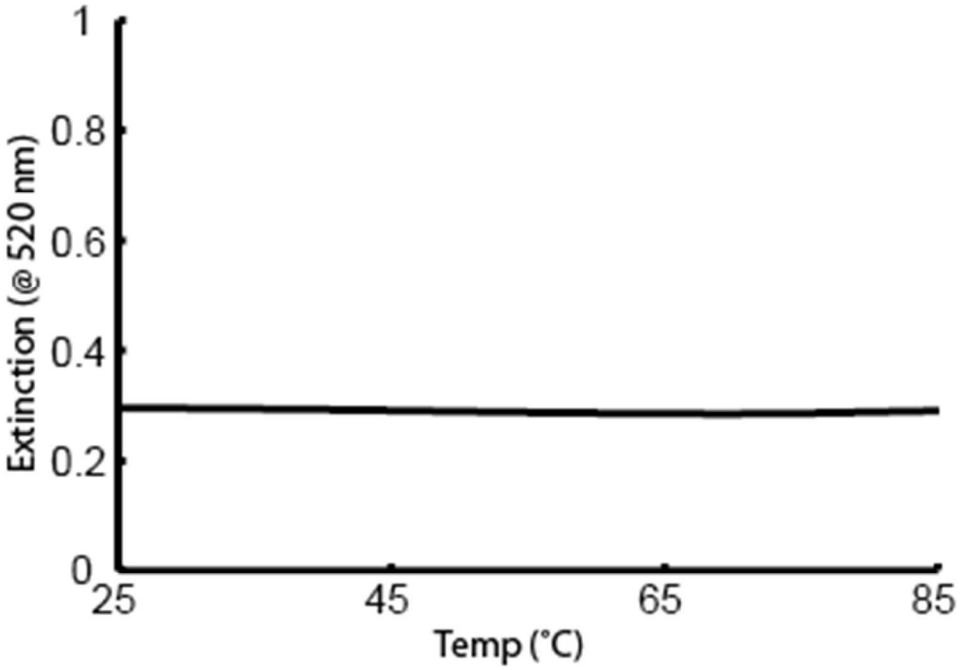

Figure S10: Melting profile of MOF nanoparticle-DNA conjugates and Au nanoparticles functionalized with non-complementary DNA.

Section S10: ^{32}P Radiolabelling of Nucleic Acid-MOF Nanoparticle Conjugates

Caution ^{32}P is a radioactive hazard. Proceed with caution.

DBCO-DNA (30 nmol) was dissolved in 56 µL of NANOpure water. To the DBCO functionalized DNA, 10 µl of Kinase 10x Buffer (Promega), 4 µL of T4 polynucleotide kinase (Promega), and 30µl of [γ- 32P] ATP (at 3,000 Ci/mmol, 10 mCi/ml, 50 pmol total) (Perkin Elmer) were added The solution was shaken on a mechanical shaker for 30 minutes at 37 ˚C. The solution was desalted utilizing a NAP-10 column (GE Healthcare). The ^{32}P labeled strands were utilized to functionalize MOF nanoparticles under identical conditions as those reported above.

The radioactivity of radiolabelled nucleic acid-MOF nanoparticle conjugates functionalized with ^{32}P was measured utilizing a TriCarb 2910 TR liquid scintillation counter (Perkin Elmer). A standard curve (counts per second vs absorbance) was generated to determine the DNA surface coverage of MOF nanoparticle-DNA conjugates.

Section S11: Confocal Microscopy

All microscopy was performed using an SP5 laser scanning confocal microscope. Cellular images were obtained by culturing HeLa cells in supplemented Dulbecco's Modified Eagle Medium (DMEM, Life Technologies) at approximately 30% confluency in Nunc Lab-Tek II borosilicate-bottom chamber slides (Thermo Scientific). Cells were allowed to attach for 24 hours, after which they were suspended in OptiMEM and treated with either DNA or 14 nm MOF-NPs at a concentration of 100 nM (DNA basis). After 24 hours the cells were washed once with OptiMEM and suspended in DMEM containing Hoechst 33258 (Life Technologies). Images were taken using a 100x oil-immersion lens. Images of MOF-NPs were obtained with similar microscope settings by suspending MOF nanoparticles in water on a borosilicate slide cover. MOF nanoparticles prior to functionalization showed no significant fluorescence (Figure S11).

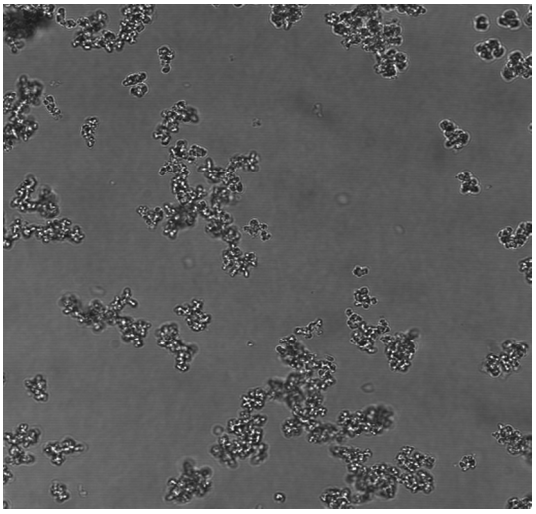

Figure S11: Confocal microscopy image of 540 nm MOF nanoparticles prior to DNA functionalization.

Section S12: Cell Culture

HeLa cells were cultured in DMEM supplemented with 10% Fetal Bovine Serum (Atlanta Biologicals) and 1% Penicillin/streptomycin (Life Technologies).

For quantitative uptake via flow cytometry (Guava Easycyte 8HT), HeLa cells were cultured on 13 mm diameter tissue culture coated slide covers and were allowed to attach for 24 hours. The slide covers were then transferred to a 24-well culture dish containing OptiMEM (Life Technologies). For flow cytometry experiments, cells were treated with DNA or MOF-NPs at a concentration of 100 nM DNA for 24 hours, after which they were washed once with OptiMEM and trypsinized. Analogous procedures were followed for ICP-MS experiments with cells treated with a solution containing 1 x 10^{-7} mol/mL of Zr for both the unfunctionalized and functionalized MOF-NPs. ICP-MS was conducted by quantifying the number of cells contained in each well via flow cytometry. Following cell counts, cells were turned into pellets by centrifugation and digested in nitric acid at 60 ˚C for ICP-MS analysis. Cell viability experiments were carried out utilizing a Presto Blue assay after treating cells with DNA or MOF-NPs at a concentration of 100 nM DNA for 24 hours

Section S13: References

1) Macfarlane, R. J.; Lee, B.; Jones, M. R.; Harris, N.; Schatz, G. C.; Mirkin, C. A. *Science.* **2011**, *334*, 204.
2) Kim, M.; Cahill, J. F.; Su, Y.; Prather, K. A.; Cohen, S. M. *Chemical Science* **2012**, *3*, 126.
3) Cavka, J. H.; Jakobsen, S.; Olsbye, U.; Guillou, N.; Lamberti, C.; Bordiga, S.; Lillerud, K. P. *J. Am Chem. Soc.* **2008**, *130*, 13850.
4) Materials studio version 5.0, 2012, Accelrys Software version 6.1