Supporting Information

**Cell penetrating peptide together with PEG-modified mesostructured silica nanoparticles promotes mucous permeation and oral delivery of therapeutic proteins and peptides**

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Figure S1. FT–IR spectra of intermediates in PEG-modification.

Figure S2. $N_2$ adsorption–desorption isotherms of MSN, LMSN, LMSN-PEG$_{4k}$ and LMSN-PEG$_{10k}$. 
Figure S3. *In vitro* CPP release behaviors of ALG-coated (a) CPP@LMSN-PEG\(_{4k}\) (ALG@CPP@LMSN-PEG\(_{4k}\)) and (b) CPP@LMSN-PEG\(_{10k}\) (ALG@CPP@LMSN-PEG\(_{10k}\)).

Figure S4. Cytotoxicity of specific endocytic inhibitors.
Figure S5. LSCM images of HT29 cells incubated with LMSN-PEG$_{4k}$ and LMSN-PEG$_{10k}$ with or without CPP-involvement under specific lysosome (LYSO) or endoplasmic reticulum (ER) trackers (scale bar: 10 μm).
Figure S6. Cytotoxicity of specific organelle inhibitors.

Figure S7. LSCM images of duodenum, jejunum and ileum and colon after administration with LMSN system (blue, DAPI-stained nucleus; green, FITC-labeled silica NPs; red, Cy3-labeled cargo; yellow, co-localization of silica NPs and cargos) (scale bar: 200 μm).
**Figure S8.** SEM images of lyophilized ALG-coated LMSN (a and b), and a small number of silica nanoparticles were hidden behind ALG layers in the shallow depth (c and d).

**Figure S9.** Images of lyophilized tablets (a) before and (b) after incubation in medium at pH values of 1.2 (left) and 7.4 (right).
**Figure S10.** *In vitro* RGH release behaviors of (a) ALG-coated RGH@LMSN-PEG_{4k} (ALG@RGH@LMSN-PEG_{4k}) and (b) RGH@LMSN-PEG_{10k} (ALG@RGH@LMSN-PEG_{10k}).

**Figure S11.** Flow cytometry analysis of cellular uptake and mean fluorescent intensity of Caco-2 cells after incubation by CPP/TPP/NP with ALG-coating or dissociated ALG-coating (*p < 0.05, compared with corresponding control groups).
Figure S12. SEM images of lyophilized LMSN incubated under simulated gastric fluid and simulated intestinal fluid for 2, 6, 12 and 24 h (scale bar: 500 or 100 nm).
Figure S13. Circular dichroism spectra of released RGH samples in (a) RGH@LMSN-PEG_{4k} and (b) RGH@LMSN-PEG_{10k}.

Figure S14. Cytotoxicity of RGH, CPP and ALG solutions.
### Table S1. Zeta potential of silica nanoparticles and their preparations (mV).

<table>
<thead>
<tr>
<th></th>
<th>LMSN</th>
<th>LMSN-PEG(_{4k})</th>
<th>LMSN-PEG(_{10k})</th>
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<tbody>
<tr>
<td>NP</td>
<td>-31.8 ± 5.51</td>
<td>-18.2 ± 6.56</td>
<td>-13.6 ± 5.67</td>
</tr>
<tr>
<td>RGH@NP</td>
<td>-18.6 ± 7.58</td>
<td>-11.5 ± 4.62</td>
<td>-5.91 ± 6.23</td>
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<tr>
<td>CPP@NP</td>
<td>23.9 ± 6.18</td>
<td>11.3 ± 4.63</td>
<td>1.59 ± 5.00</td>
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<tr>
<td>CPP/TPP/NP</td>
<td>14.9 ± 3.78</td>
<td>10.1 ± 4.77</td>
<td>0.935 ± 4.76</td>
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<tr>
<td>ALG-coated CPP/TPP/NP</td>
<td>-16.4 ± 4.08</td>
<td>-18.9 ± 4.52</td>
<td>-35.3 ± 8.07</td>
</tr>
</tbody>
</table>

### Table S2. RGH and CPP loading in ALG-coated CPP/TPP/NP.

<table>
<thead>
<tr>
<th></th>
<th>CPP/TPP/LMSN</th>
<th>CPP/TPP/LMSN-PEG(_{4k})</th>
<th>CPP/TPP/LMSN-PEG(_{10k})</th>
</tr>
</thead>
<tbody>
<tr>
<td>RGH loading (DL %)</td>
<td>1.528</td>
<td>1.188</td>
<td>1.108</td>
</tr>
<tr>
<td>CPP loading (DL %)</td>
<td>0.754</td>
<td>0.739</td>
<td>0.712</td>
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