Anti-miRNA delivery systems based on self-assembled nanostructure

Yu Zhang, Ph.D. Candidate
Department of Biopharmaceutical Sciences
University of Illinois at Chicago
yzhang74@uic.edu
Supramolecular self-assemblies

http://chemwiki.ucdavis.edu/
http://captain-nitrogen.com/
Nanoscale, 2013, 5, 7098
Peptide based nucleic acids delivery

<table>
<thead>
<tr>
<th>Protein</th>
<th>Functional peptide</th>
<th>Sequence</th>
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</thead>
<tbody>
<tr>
<td>TAT [HIV]</td>
<td>Tat and related peptides</td>
<td>GRKKRRQRRRPPQ</td>
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<tr>
<td></td>
<td>HIV-1 Tat (48–60)</td>
<td>GRRRRRRRRRRPPQ</td>
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<tr>
<td></td>
<td>R9-Tat</td>
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<td></td>
<td>Arginine-rich RNA binding peptides</td>
<td>TRQARRNRRRRWRERQQR</td>
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<tr>
<td></td>
<td>HIV-1 Rev-(34–50)</td>
<td>Fluo-RRRRRRRW-NH₂</td>
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<tr>
<td></td>
<td>R7W</td>
<td>Fluo-GRKKRRQQRRRPWQ-NH₂</td>
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<td></td>
<td>TatP59W</td>
<td>RRRRNTRRRRRRVR</td>
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<td></td>
<td>FHV Coat-(35–49)</td>
<td>KMTRAQRRAAARRNRTAR</td>
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<td>BMV Gag-(7–25)</td>
<td>TRRQRTARRRNR</td>
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<td>HTLV-II REX-(4–16)</td>
<td>KLTRAQRRAAARKNKNRTR</td>
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<tr>
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<td>CCMV Gag-(7–25)</td>
<td>NAKTRRHERRRRKLAIER</td>
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<td>P22 N-(14–30)</td>
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</tr>
</tbody>
</table>
Anti-miRNA deliver systems based on self-assembled nanostructure

- Polyplexes
  octaarginine complexation with anti-miRNA

- Micelleplexes
  Polyarginine bearing polymeric micelle complexation with anti-miRNA
Hypothesis: Octaarginine (R₈) can noncovalently form nanoscale complexes with single stranded anti-miRNA and mediate anti-miRNA delivery to glioblastoma and achieve efficient miRNA silencing effect.
miRNA is an emerging field
Dual roles of miRNAs in cancer

miRNA as Tumor Suppressor
- Overexpression of oncogenic targets
- Downregulation of TS miRNAs

miRNA as Oncogene
- Overexpression of oncogenic miRNAs
- Downregulation of TS genes

Cancer initiation & progression
- Angiogenesis
- Proliferation
- Invasion
- Apoptosis

miRNA “replacement” therapy

miRNA “knockdown” therapy

InteRNA Technologies
New hope brought in by miRNAs for cancer therapy

- Cancer is “signaling pathway” disease
- miRNAs can regulate a broad network of genes
- miRNAs were identified as key oncogenic targets in cancer stem cells
miRNA-21 and glioblastoma
miRNA-21 and glioblastoma

Glioblastoma multiforme (GBM) is a fatal brain tumor with an annual incidence of approximately 5 in 100,000 people.  

An analysis on clinical patient samples showed that miR-21 is consistently overexpressed in glioblastoma tumor tissue but not in adjacent normal brain parenchyma, and the miR-21 levels correlated significantly with the grade of gliomas.  

MiRNA-21 has been shown to function as an oncogenic miRNA in glioblastoma through modulating a network of key tumor-suppressive pathways in glioblastoma cells.  

Overexpression of miRNA-21 is also associated with poor prognosis in glioblastoma patients.  

Anti-miR-21 was used to sensitize glioblastoma cell toward PTX in vitro.
Challenges of RNA delivery carrier design

Effect of PEGylation
- Increase steric stability
- Decrease unspecific interaction
- Decrease RNA loading capacity
- Low delivery efficiency

Complexation-decomplexation
- RNA protection
- Stability
- Slow release
- Low efficiency

Nanomedicine (2011) 6(4), 715–728
Physicochemical characterization of anti-miRNA/R\textsubscript{8} complexes

The importance of nanoparticle ζ-potential for gene delivery carrier

A. Nucleic acid loading capacity
B. Nanoparticle-nanoparticle interactions
C. Nanoparticle-cell interactions
D. Part of the initial nanoparticle system-cell targeting process

Malvern Instruments Workshop –09/21/2011
Cellular association of anti-miRNA/Rg complexes

miR-21 targeted gene expression

Anti-miR-21/R8 complexes inhibit cell migration