

## Electronic Supplementary Information

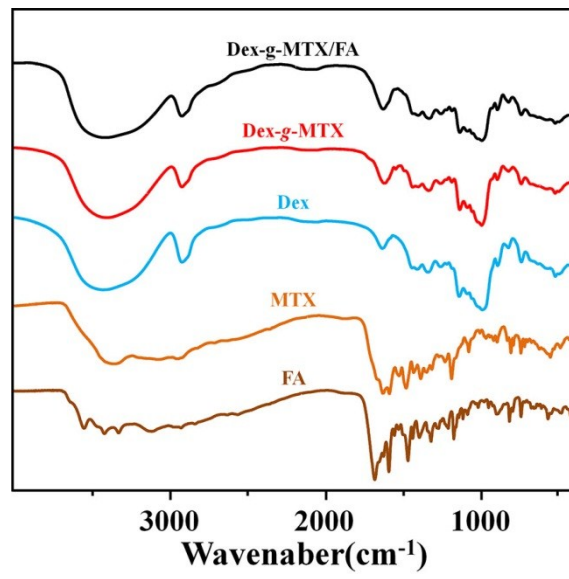
### Activated macrophage-targeted dextran–methotrexate/folate conjugate prevents deterioration of collagen-induced arthritis in mice

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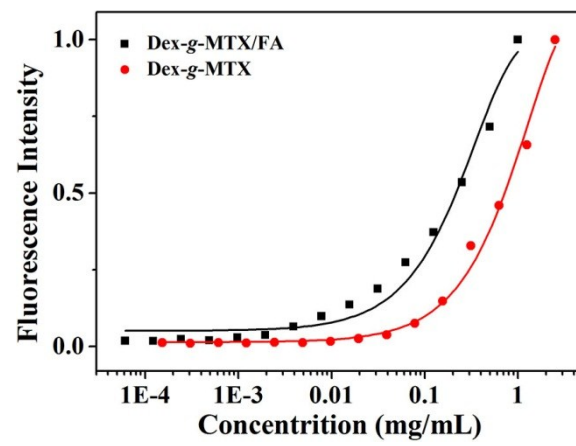
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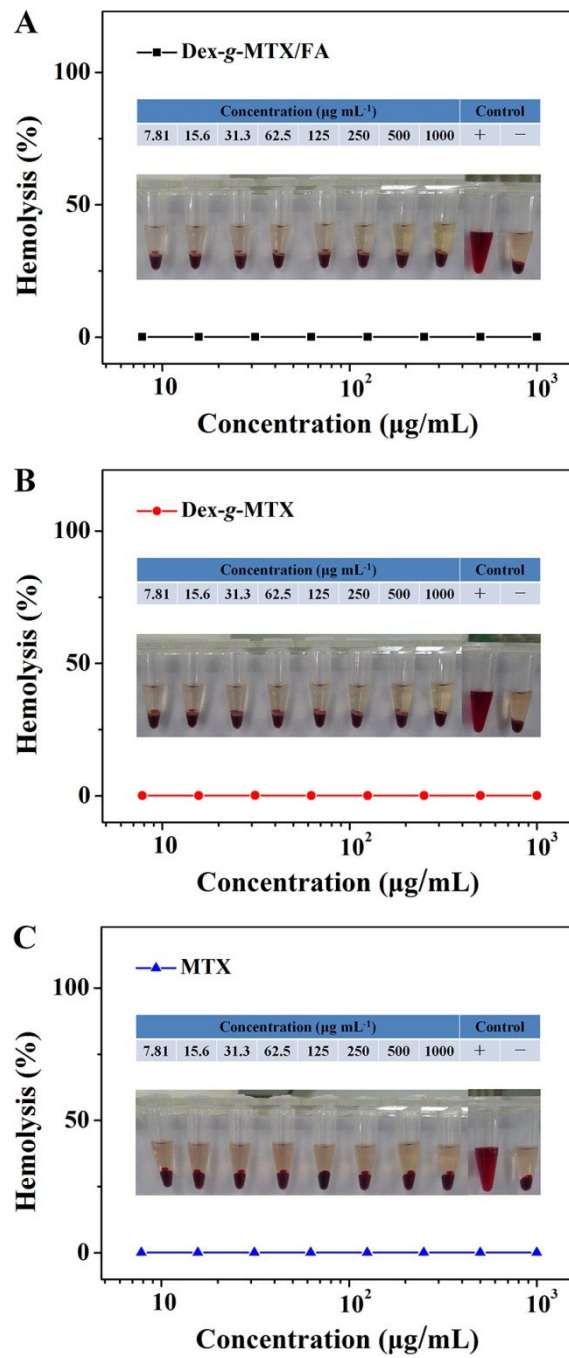
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**Fig. S1** FT-IR spectra of Dex-g-MTX/FA, Dex-g-MTX, Dex, MTX, and FA.



**Fig. S2** Critical micelle concentrations (CMCs) of Dex-g-MTX/FA and Dex-g-MTX.



**Fig. S3** Hemolysis of Dex-g-MTX/FA (A), Dex-g-MTX (B), and free MTX (C). Data were presented as mean  $\pm$  standard deviation ( $n = 3$ ).

**Table S1** Morphological features of synovium

Feature	Score
A. Hyperplasia or enlargement of synovial lining cell layer	
1. Absent	0
2. Slight enlargement (two to three cell layers). Giant cells are very rare	1
3. Moderate enlargement (four to five cell layers). Some giant cells or lymphocytes	2
4. Strong enlargement (more than six cell layers). Giant cells and lymphocytes are frequent	3
B. Inflammatory infiltration	
1. Absent	0
2. Slight inflammatory infiltration (diffusely located single cells and small perivascular aggregates of lymphocytes and/or plasma cells)	1
3. Moderate inflammatory infiltration (perivascular and/or superficial lymphatic aggregates, and small sized lymphatic follicles without germinal center may be observed)	2
4. Strong inflammatory infiltration (lymphatic follicles with germinal center and/or confluent subsynovial lymphatic infiltration)	3
C. Activation of synovial stroma/pannus formation	
1. Absent	0
2. Slight synovial stroma activation (low cellularity with slight edema, slight fibrosis with some fibroblast, no giant cells)	1
3. Moderate synovial stroma activation (moderate cellularity with a moderate density of fibroblasts, endothelial cells, and giant cells may be detected)	2
4. Strong synovial stroma activation (high cellularity with dense distribution of fibroblasts and endothelial cells, and giant cells are abundant)	3

**Table S2** Modified OARSI scores to evaluate the cartilage status microscopically

Feature	Score
<b>A. Structure</b>	
0. Normal	0
1. Slight surface irregularities	1
2. Moderate surface irregularities	2
3. Severe surface irregularities	3
4. Clefts/fissures into transitional zone (one-third depth)	4
5. Clefts/fissures into radial zone (two-thirds depth)	5
6. Clefts/fissures into calcified zone (full depth)	6
7. Fibrillation and/or erosion to transitional zone (one-third depth)	7
8. Fibrillation and/or erosion to radial zone (two-thirds depth)	8
9. Fibrillation and/or erosion to calcified zone (full depth)	9
10. Fibrillation and/or erosion to subchondral bone	10
<b>B. Cellularity</b>	
0. Normal	0
1. Increase or slight decrease	1
2. Moderate decrease	2
3. Severe decrease	3
4. No cells present	4
<b>C. Chondrocyte cloning</b>	
0. Normal	0
1. Several doublets	1
2. Many doublets	2
3. Doublets and triplets	3
4. Multiple cell nests	4