Gold Nanoparticles as Carriers of MicroRNA Mimics for Cancer Immunotherapy and Muscular Diseases

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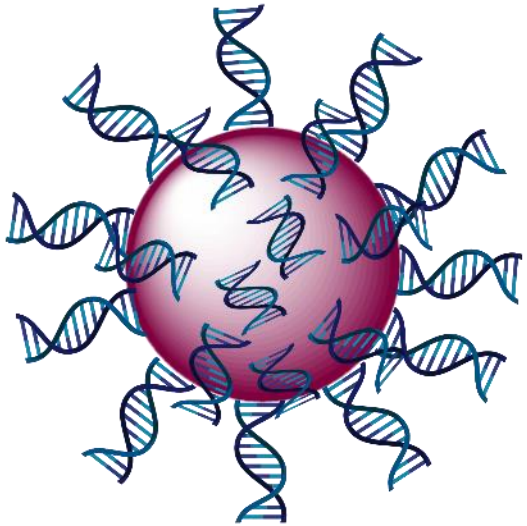
NEXT-GENERATION DELIVERY INNOVATIONS

Immunotherapy for
Cutaneous Melanoma

Immune cells

On going

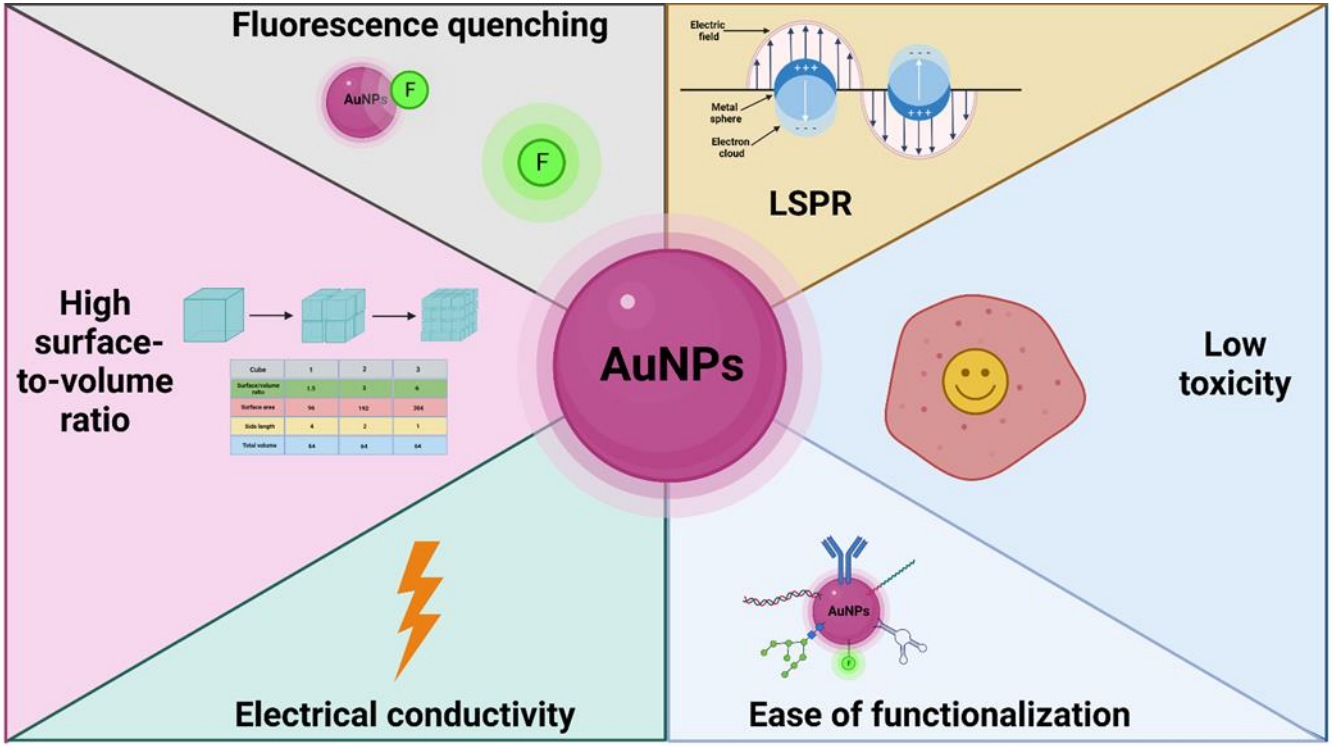


Gene regulation for
Duchenne muscular dystrophy

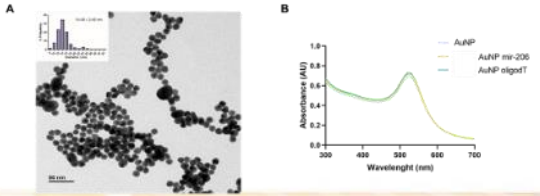
Muscle stem cells

Nat. Commun 2025, 16, 577

Gold Nanoparticles

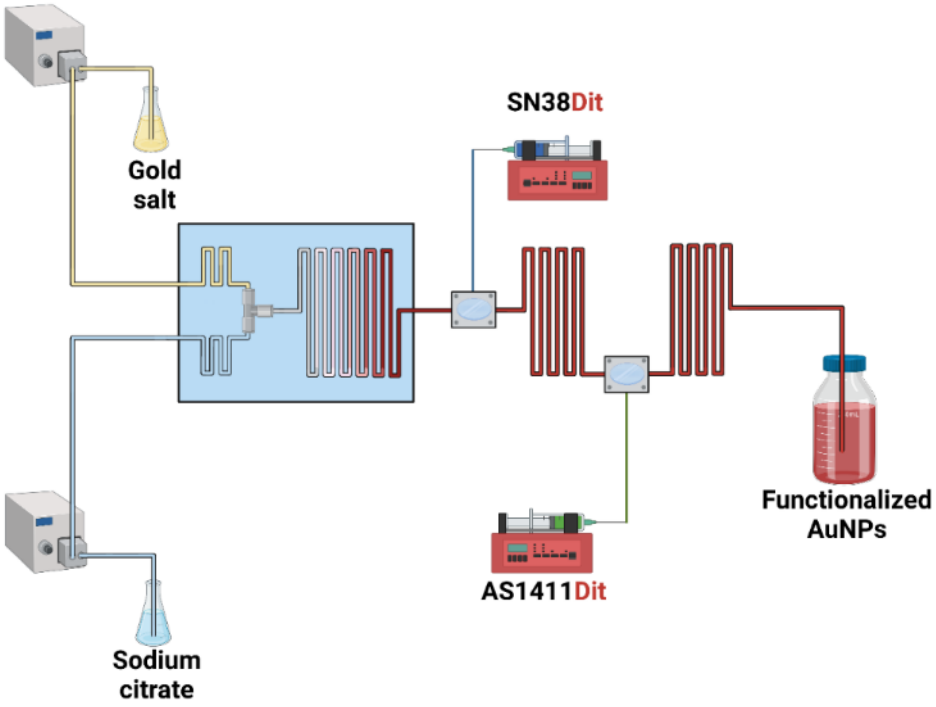


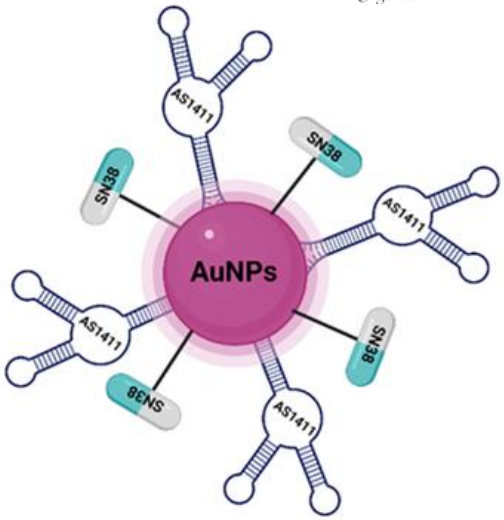
Gold Nanoparticles



Easy to prepare
Easy to functionalize
Non Toxic

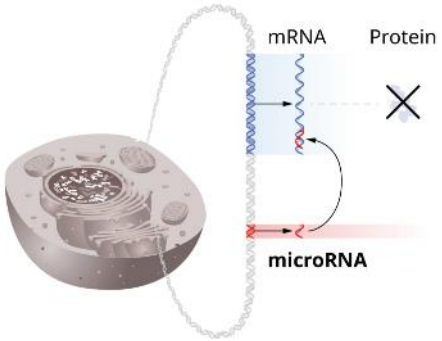
Flow Synthesis of modified AuNPs

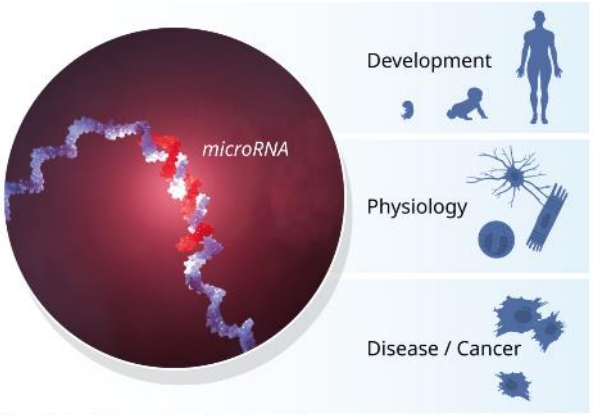




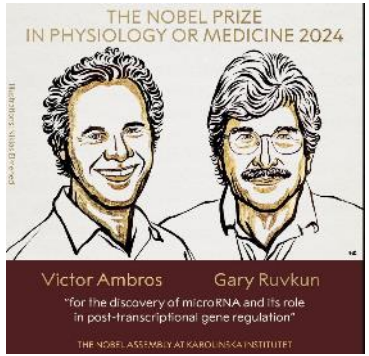
microRNAs

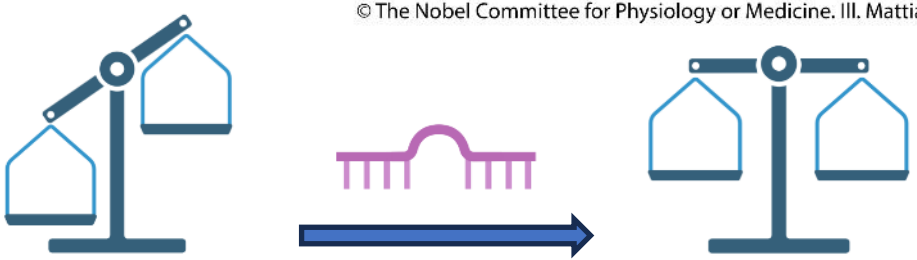
- Non-Coding RNAs (ca. 98%)
- Key in the regulation of processes
- 19-23 nt long





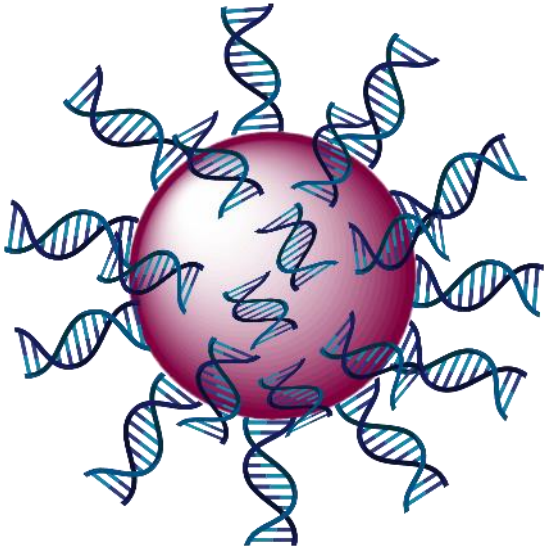
© The Nobel Committee for Physiology or Medicine. Ill. Mattias Karlén





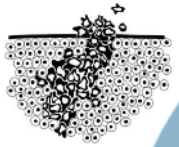
Labile
Poor biodistribution
Poor translocation to cells

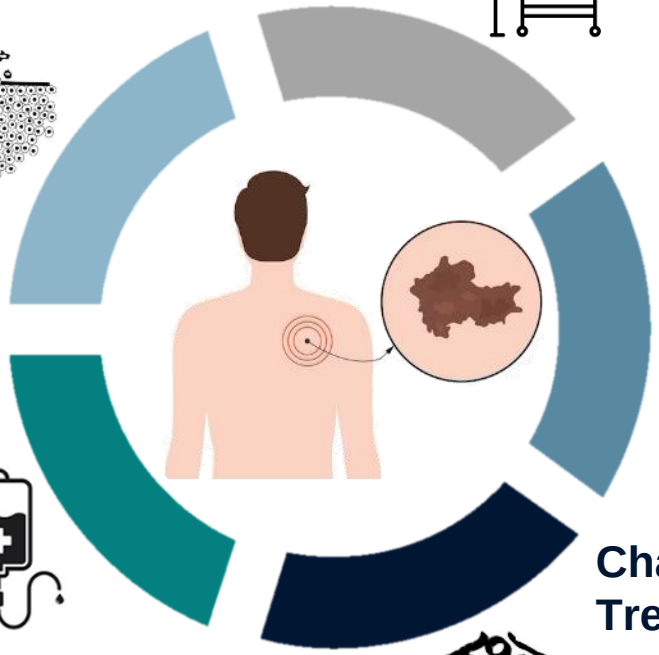
Gold Nanoparticles with miRNA mimics



Cutaneous Melanoma

Deadliest form of skin cancer: Aggressive and metastatic





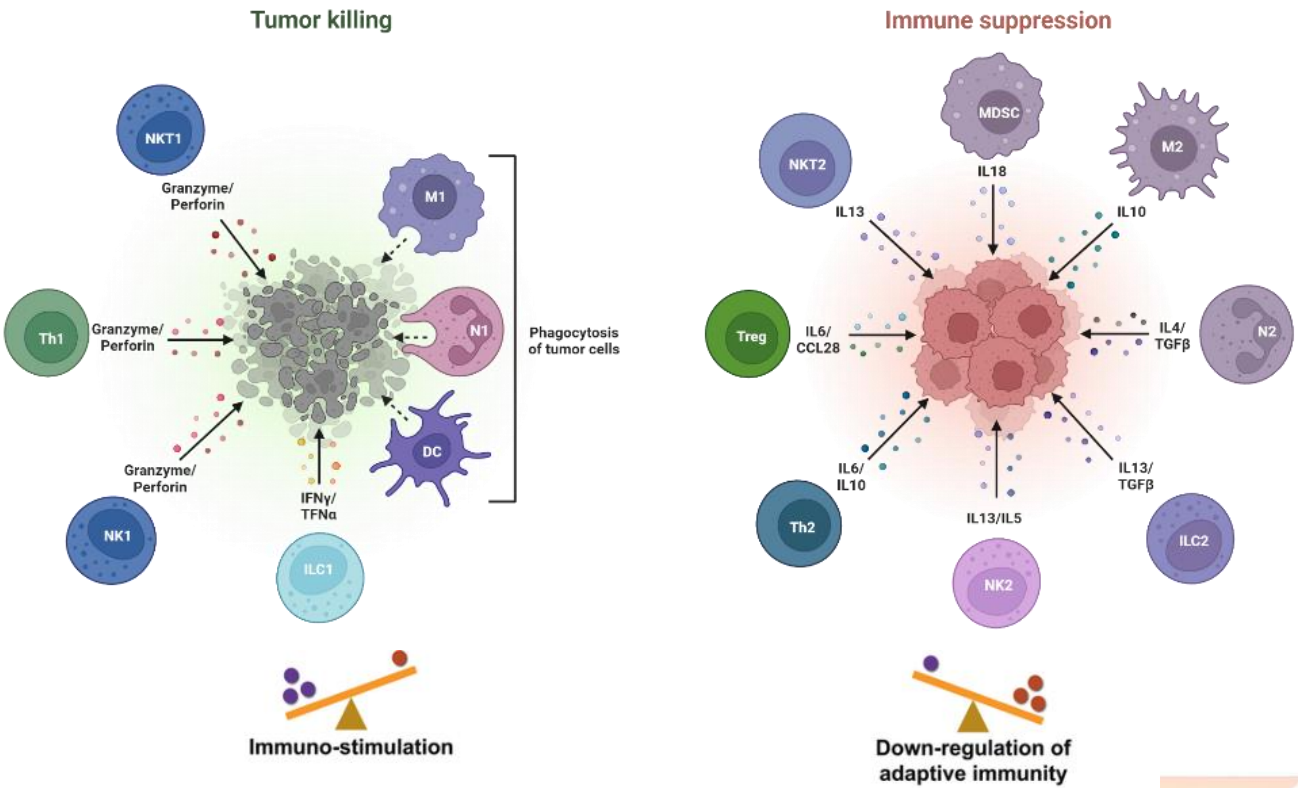
Increasing incidence and high mortality in advanced-stage

Early diagnosis is frequent, yet late cases progress rapidly

Current treatments: Surgery, immunotherapy and targeted therapy

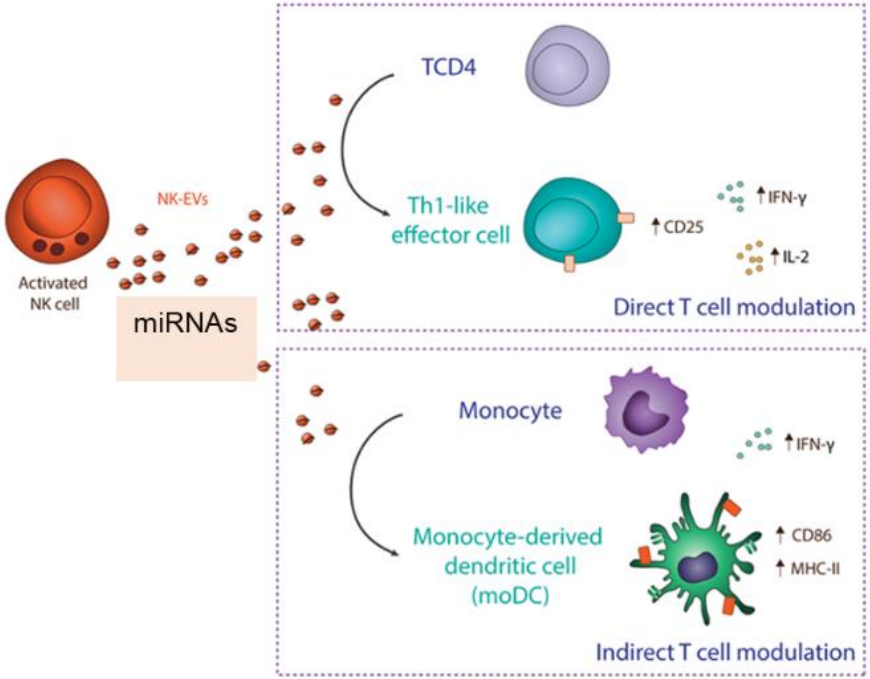
Challenges: Treatment resistance and recurrent metastasis

Immunotherapy



EV-derived miRNAs for Immunotherapy

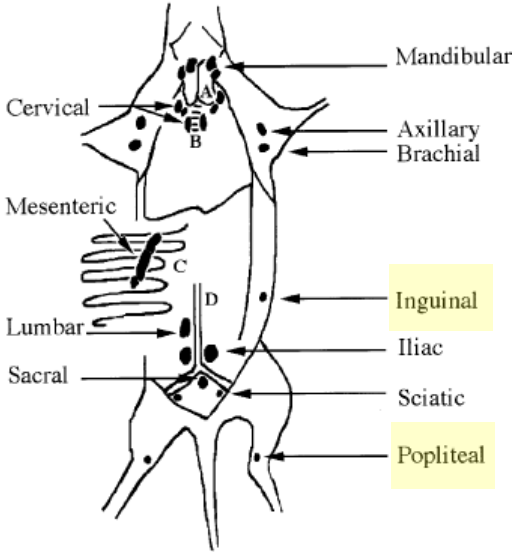
NK cells modulate immune responses by regulating T cell activity through extracellular vesicles that carry microRNAs targeting key molecules involved in Th1 responses.

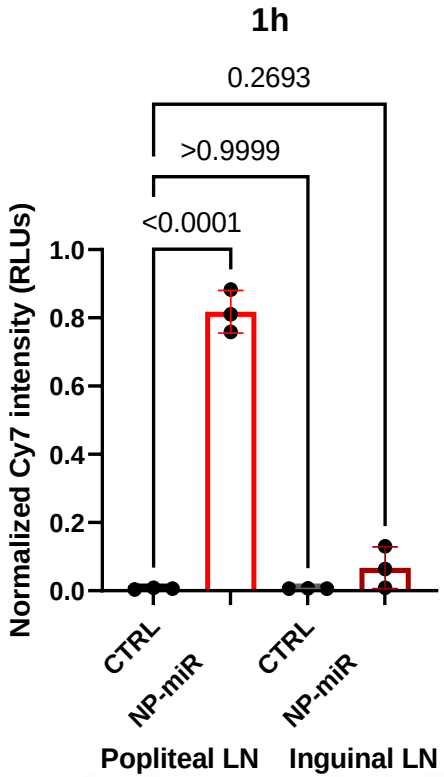


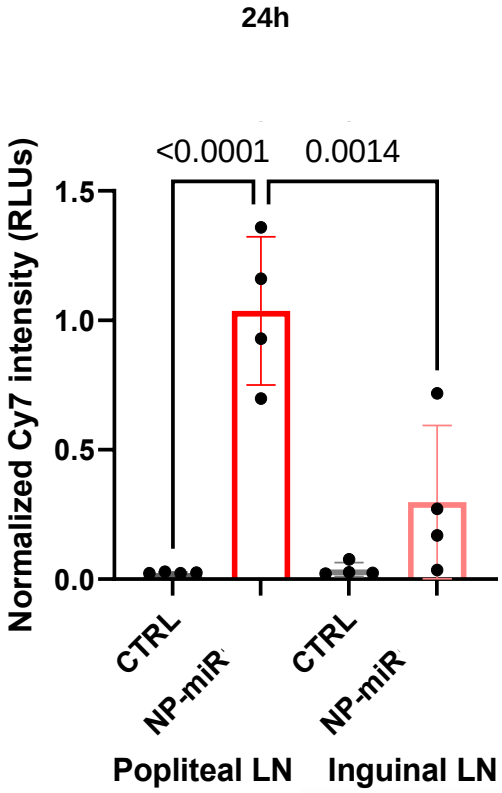
Can we modulate the anti-tumor immune response by "mimicking" NK cell-derived EVs?

Adapted from
Dosil et al., eLife, **2022**. doi: 10.7554/eLife.76319

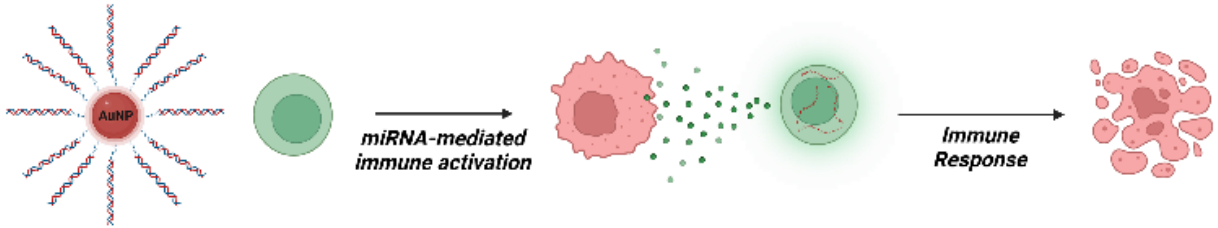
Lymphatic dissemination promotes the localization of NPs in the popliteal node



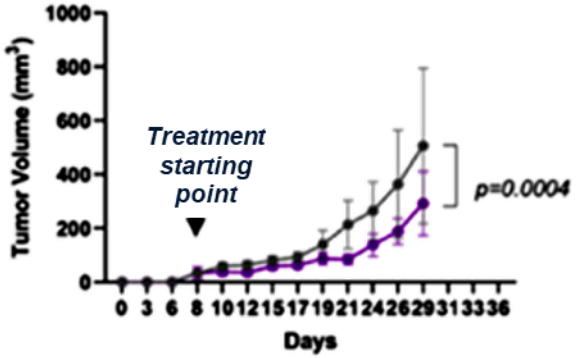




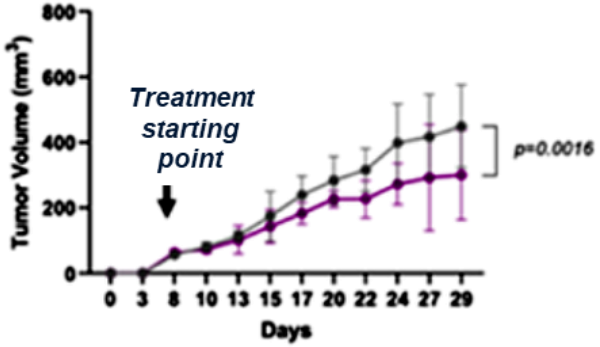
AuNP-miRNA for IT in melanoma models



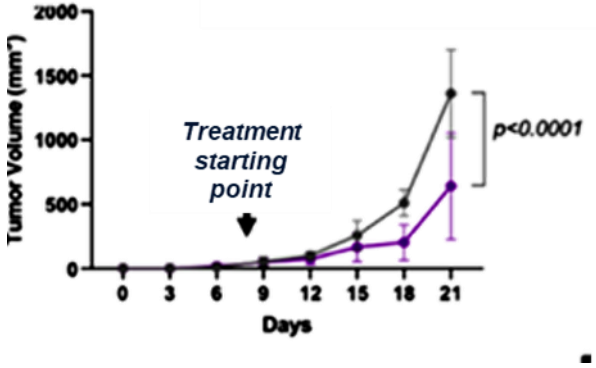
YUMM 2.1 (not IT Resistant)



YUMM 1.1 (IT Resistant)



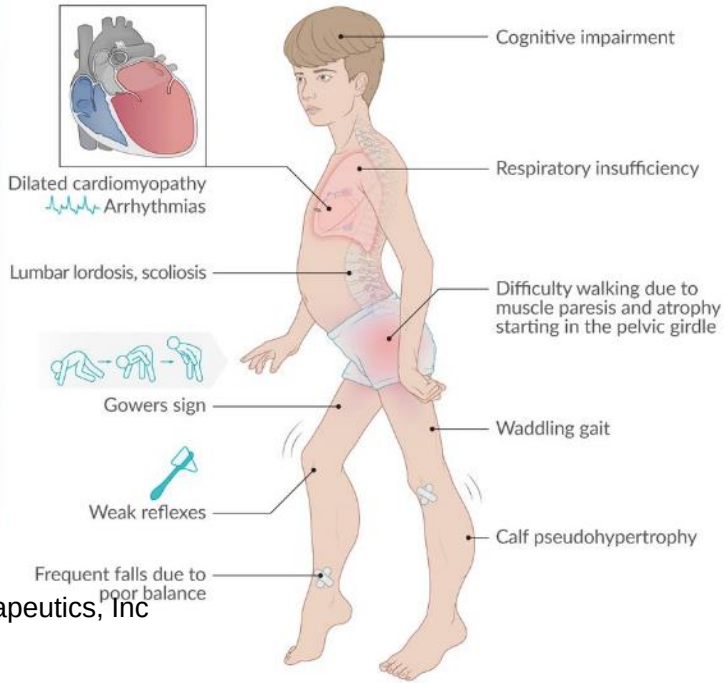
B16-F10 cell (highly metastatic)



Duchenne Muscular Dystrophy (DMD)

A devastating muscle disease due to defective Dystrophin (X-Linked recessive)

	Duchenne muscular dystrophy	Becker muscular dystrophy
Etiology	**X-linked recessive**, dystrophin gene mutation	
Dystrophin protein	Absent	Reduced
Age of onset	2–5 years	> 15 years
Symptoms	Rapid progression, inability to walk by approx. 12 years	Less severe, slower progression, cardiac involvement is more common
Diagnostics	↑↑ **Creatine kinase**, ↑ serum aldolase, genetic analysis (confirmatory test), muscle biopsy	
Treatment	Supportive, glucocorticoids	
Life expectancy	~ 30 years	~ 40–50 years



Arround 300.000 patients woldwide (rare disease)

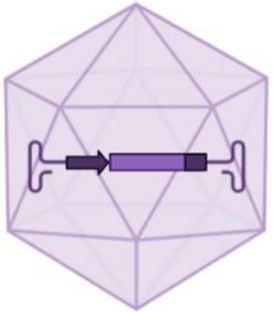
June 2023 FDA approved first gene therapy (Elevidys, Sarepta Therapeutics, Inc

https://www.amboss.com/us/knowledge/progressive-muscular-dystrophies

https://www.mda.org/disease/duchenne-muscular-dystrophy

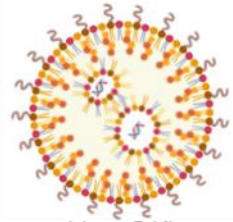
Gene Therapies

AAV



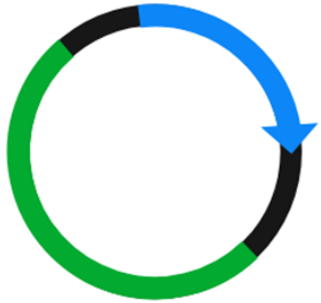
Max : 5 Kb

LNPs



Max : 5 Kb

Dystrophin



79 exons, 2,300 kilobases (kb)

11 Kb

Mini- Dystrophin

Exon Skipping

79 exons, 2,300 kilobases (kb)

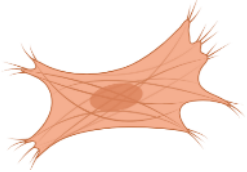
Truncated-Dystrophin (Becker)

Gene Therapies

Dystrophin

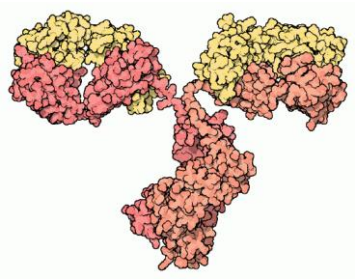
“mini”/ “truncated”-Dystrophin

Muscle Stem Cells



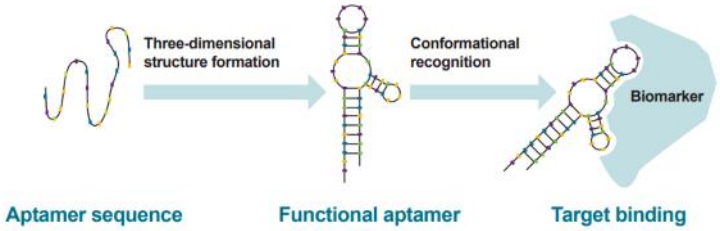
Mir-206

Aptamers



Antibody
150 kD
10-15 nm

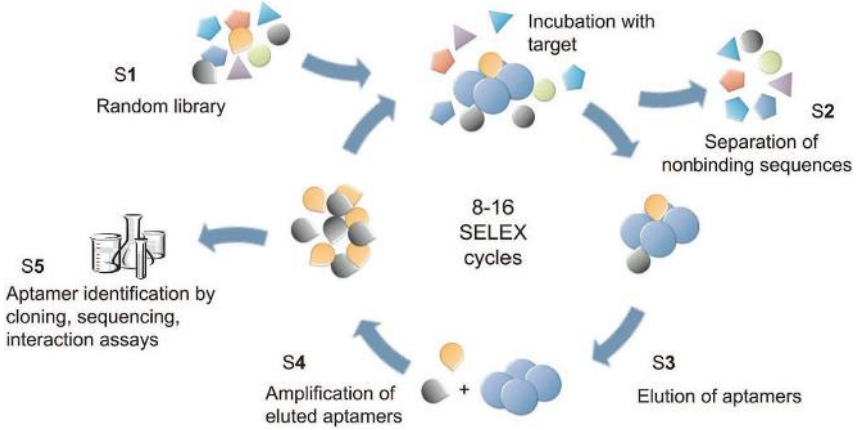
Aptamers
5-30 kD
1-3 nm



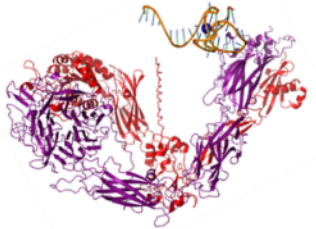
https://www.lubio.ch/

- DNA or RNA strands with high affinity
- Lenght 40-80 nts
- Can be found by SELEX

Library: 10^8 -10^{15} different sequences



Molecular Therapy - Nucleic Acids **2015**, *4*, e223.

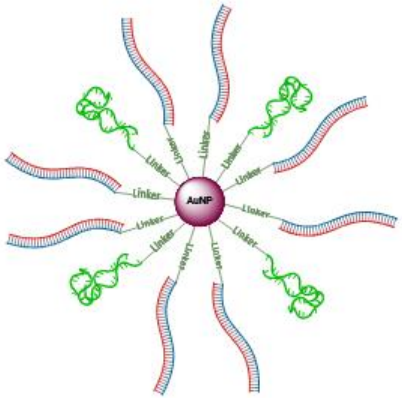


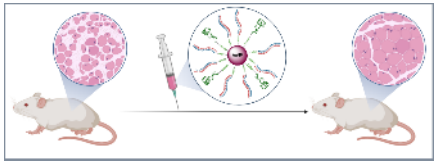
Aptamer againts $\alpha 7\beta 1$ integrin present in MSC

Therapy based on mir-206 and AuNPs

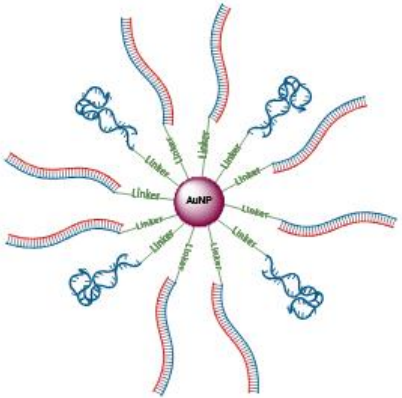
Formulations

α7β1 AuNPs



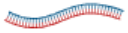


Scr AuNPs



Scramble Sequence

Targeting Aptamer (α7β1)

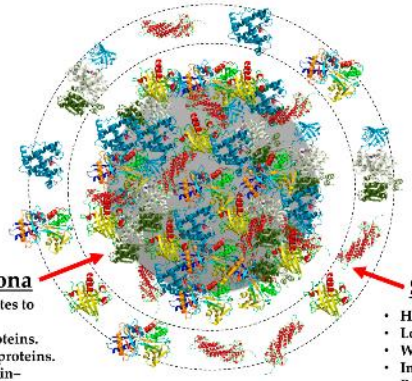


miRNA mimic (e.g., miR-206, miR-39, Oligo dT)

Gold Nanoparticle

miR-206 plays important roles in Muscular Stem Cells differentiation and in skeletal muscle regeneration.

Protein Corona

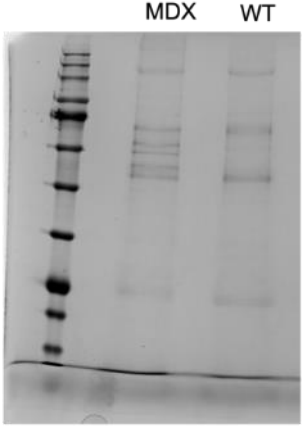


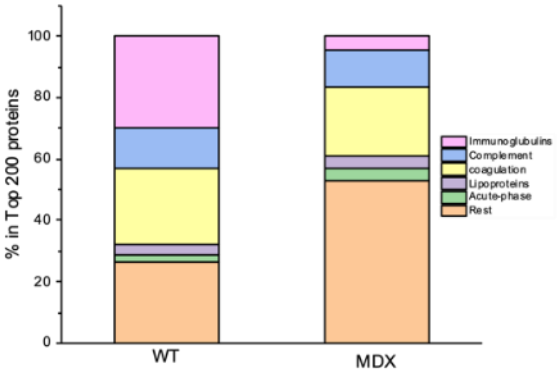
Hard Corona

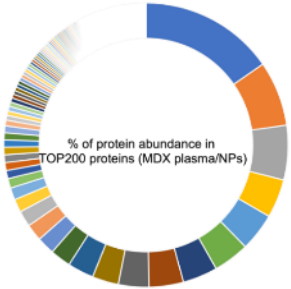
- Seconds to minutes to form.
- High affinity proteins.
- Strongly bound proteins.
- Interaction Protein–Nanoparticle.
- Low dissociation constant.

Soft Corona

- Hours to form.
- Low affinity proteins.
- Weakly bound proteins.
- Interaction Protein–Protein.
- High dissociation constant.







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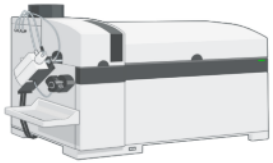
P01942 Q8K0E8 Q92111 P01872 O08677 P07759 P11276 P01029 Q91WP9 P04919 P98086 P07758 P01867 B8JJN0 Q70362 P13020 Q8BND5 P06683 Q19LI2 Q9D312 P01837 Q02357 Q9EPX2 Q922U2 P34928 P97290 E9Q6D6 P01869 Q8BH35 A0A140T8N1 Q8K182 Q07456
E9PV24 P07724 P06909 Q61838 Q00897 Q9QWK4 Q01853 D3Z2H9 A0A075B5N7 P62827 Q07235 Q8R429 Q00724 P01807 Q9QWL7 P23953 Q9JKV2 P80314 P58389 P15508 Q3SXB8 P22599 P12246 Q923D2 P50446 A0A140T8M9 O08538 Q922D8 Q8K1B8 P62270 Q6ME9 P49222
Q8VCM7 P02089 Q61646 Q00623 Q01339 P20918 P14106 P62631 A6X935 P10126 P28665 P60710 P35441 P01806 D3Z420 A0A1Y7VJN6 P00920 B2RPV6 P24270 Q61247 P11680 Q61508 P07309 Q61703 P06151 Q9WU78 B5THE2 P16294 P01592 F6YYP7 Q8BTM8 P32261

AuNPs may have a lower immunogenic profile in a dystrophic context, as compared to healthy animals

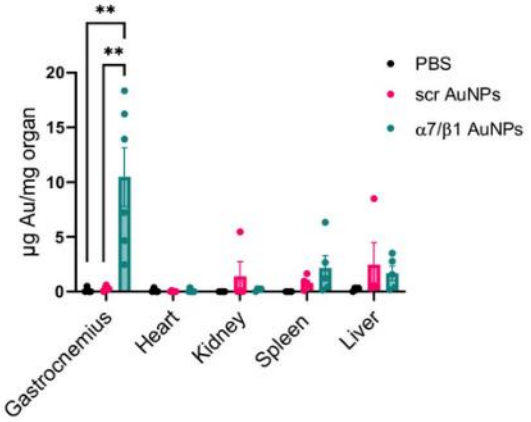
ApoE protein is low, suggesting that AuNPs may have a low liver retention

Biodistribution

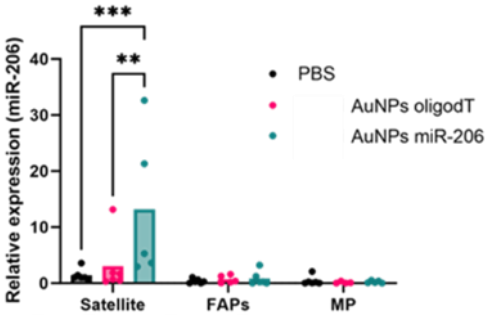


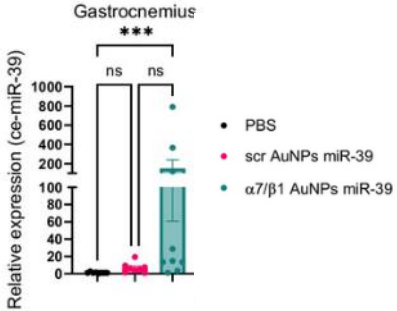
ICP-MS

RT-qPCR



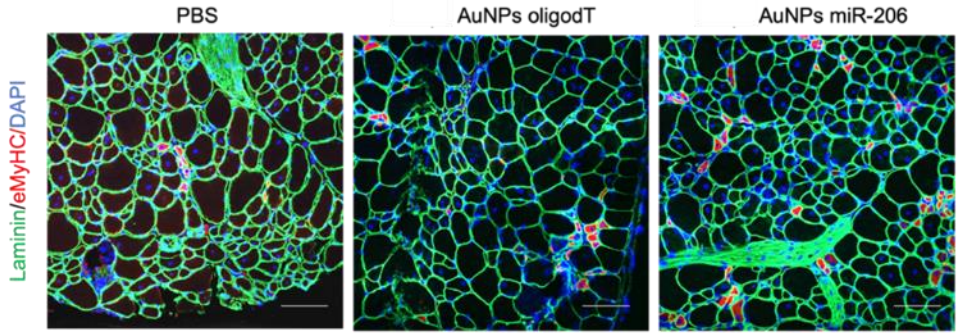
AuNPs efficiently target satellite cells in dystrophic mice

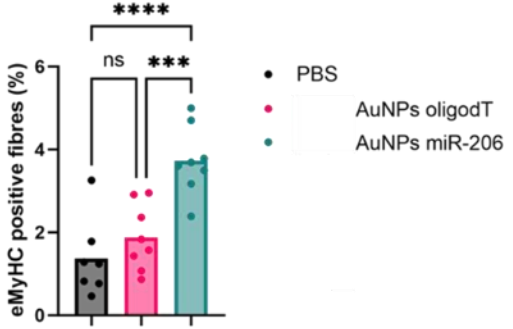




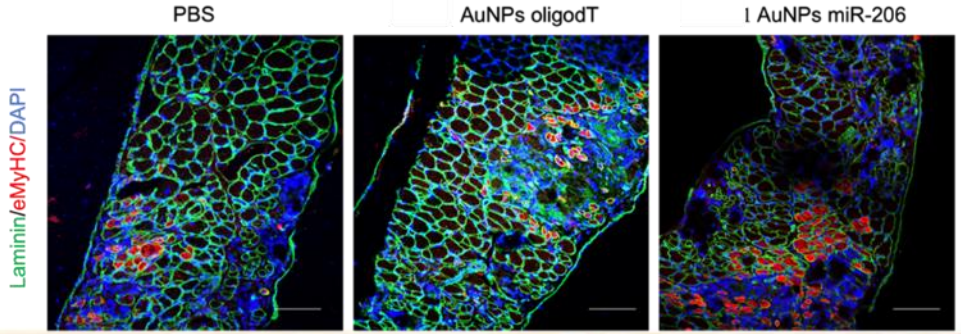
AuNPs stimulate muscle regeneration

Tibialis Anterior





Diaphragm



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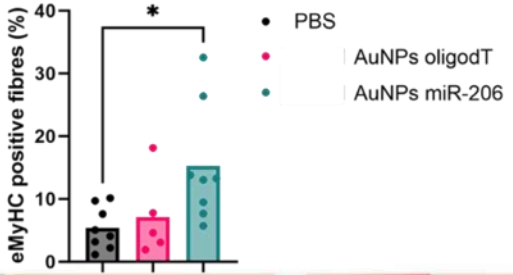
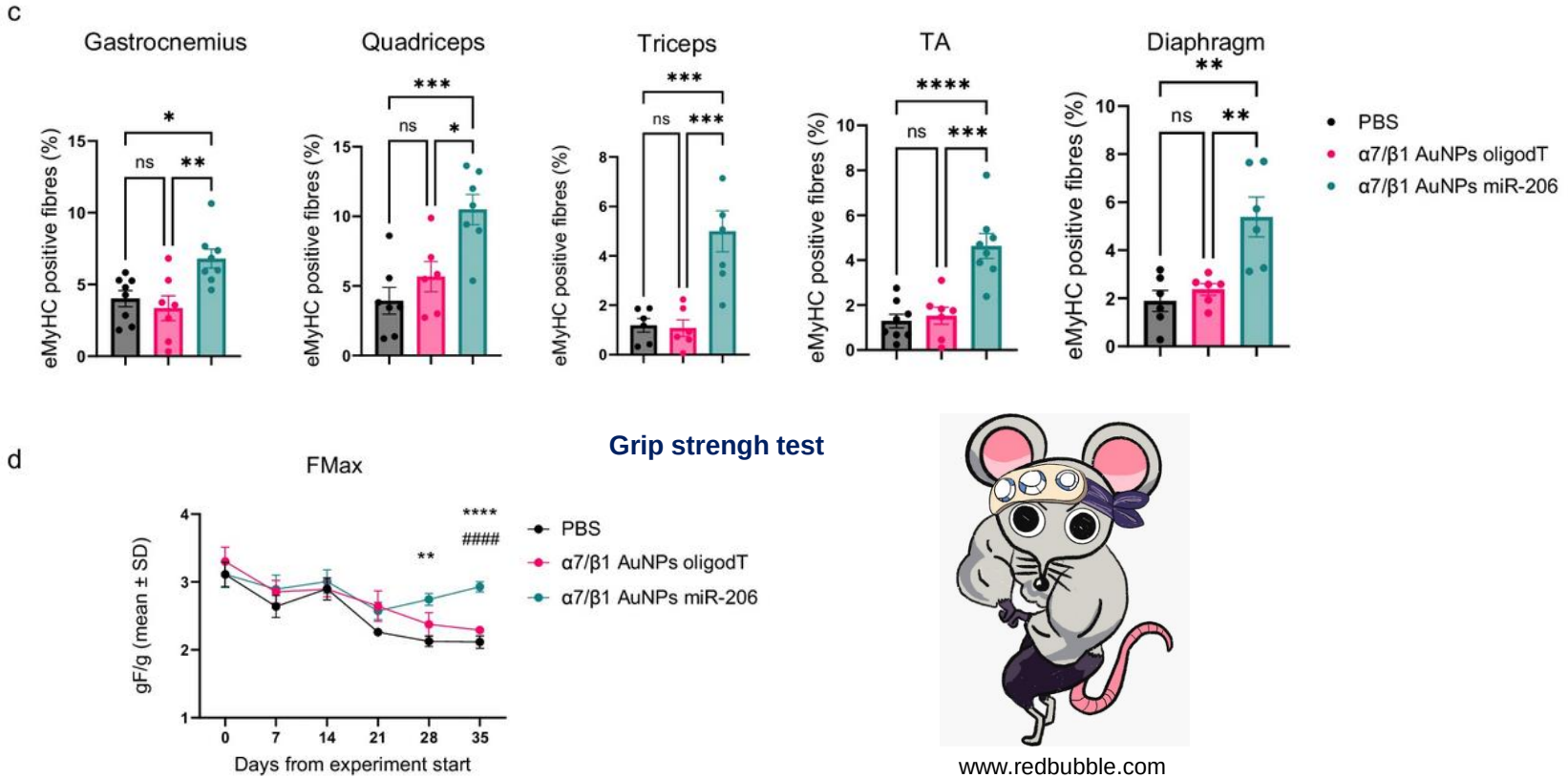


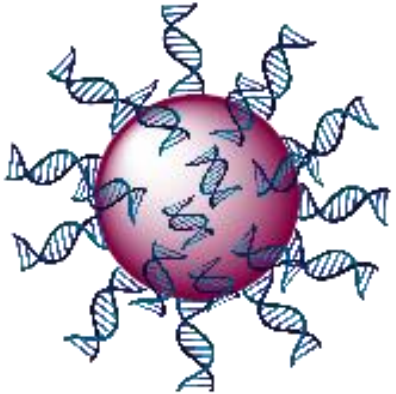
AuNPs stimulate muscle regeneration



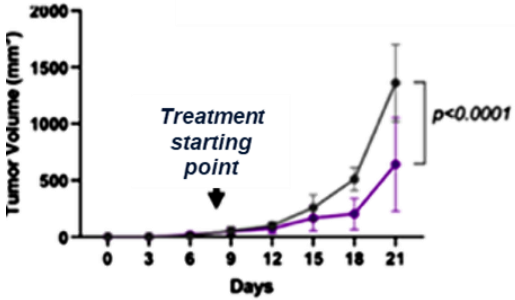
Grip strengh test

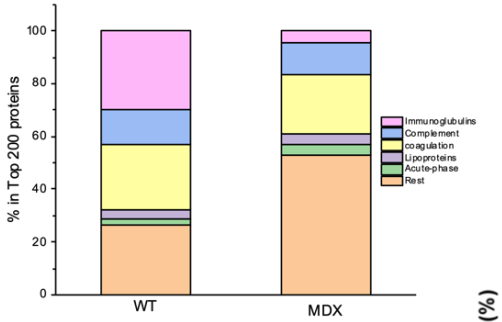
www.redbubble.com

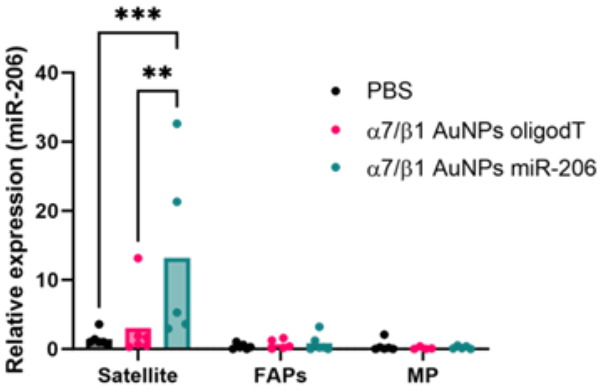
Conclusions

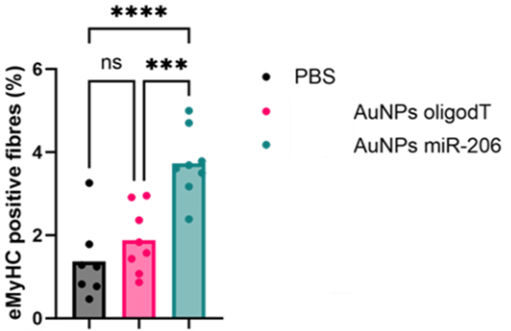


B16-F10 cell (highly metastatic)









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