Personalized Medicine: RNA therapeutics – the next revolution?

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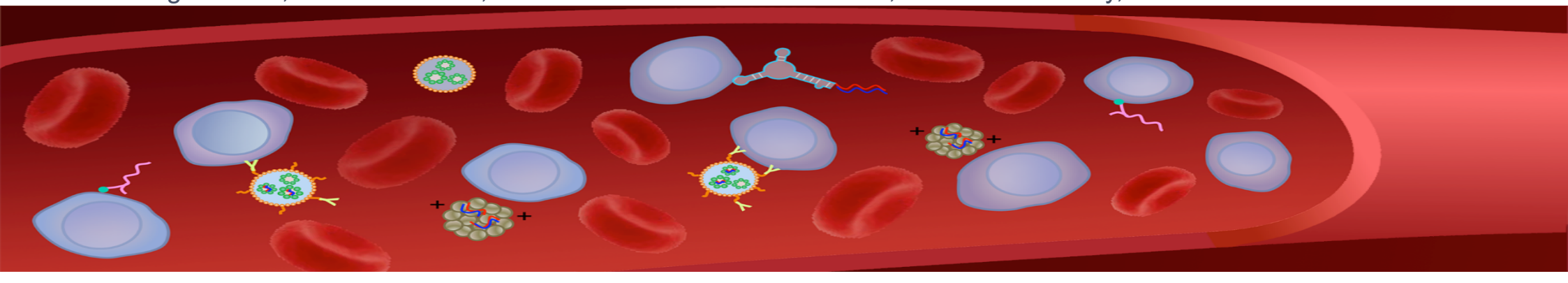


How do we define our challenges?

Leukocyte-implicated diseases

Hematopoietic

Myeloma

Leukemia

- CML
- AML
- CLL
- ALL

Lymphoma

- Hodgkin's
- NHL
- MCL

Inflammation

Autoimmune

- Ulcerative colitis
- Crohn's
- RA
- Psoriasis
- Lupus/SLE
- MS

Allergy/Asthma

GVHD

IR injury

Viral Infection

HIV

Ebola

Solid Tumors

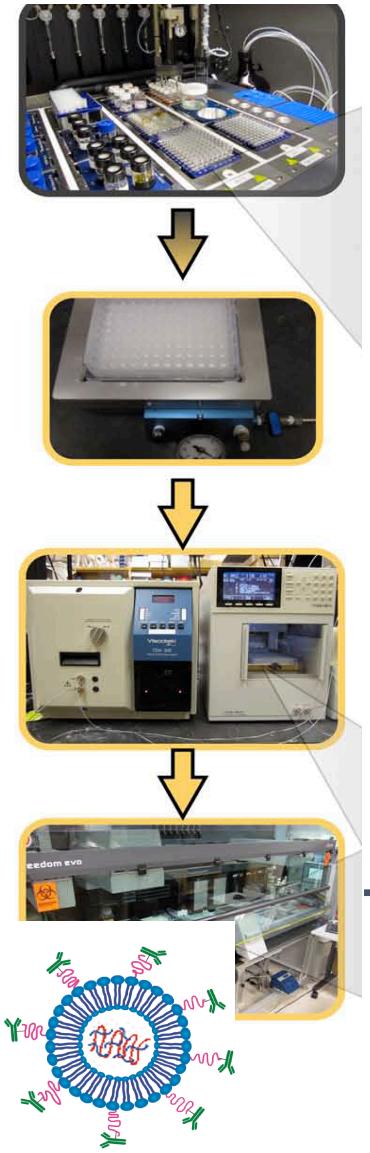
Ovarian

GBM

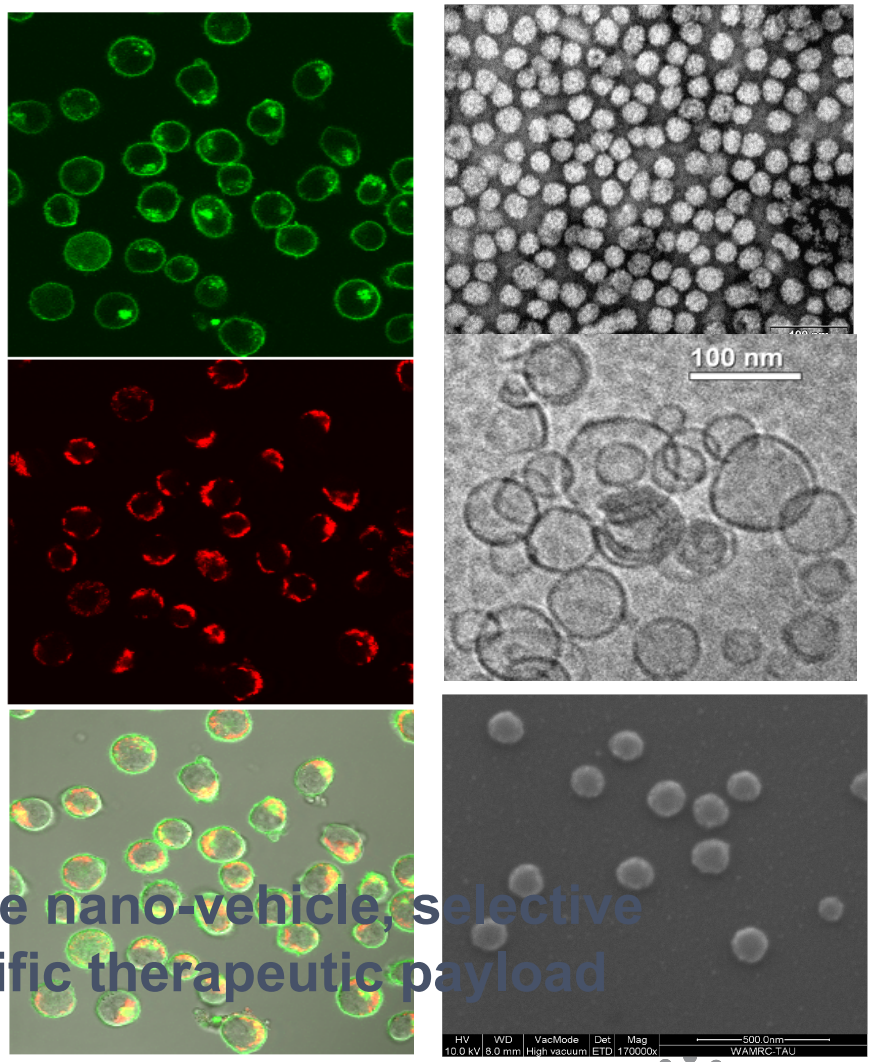
Rare Genetic diseases

Laboratory of Precision NanoMedicine

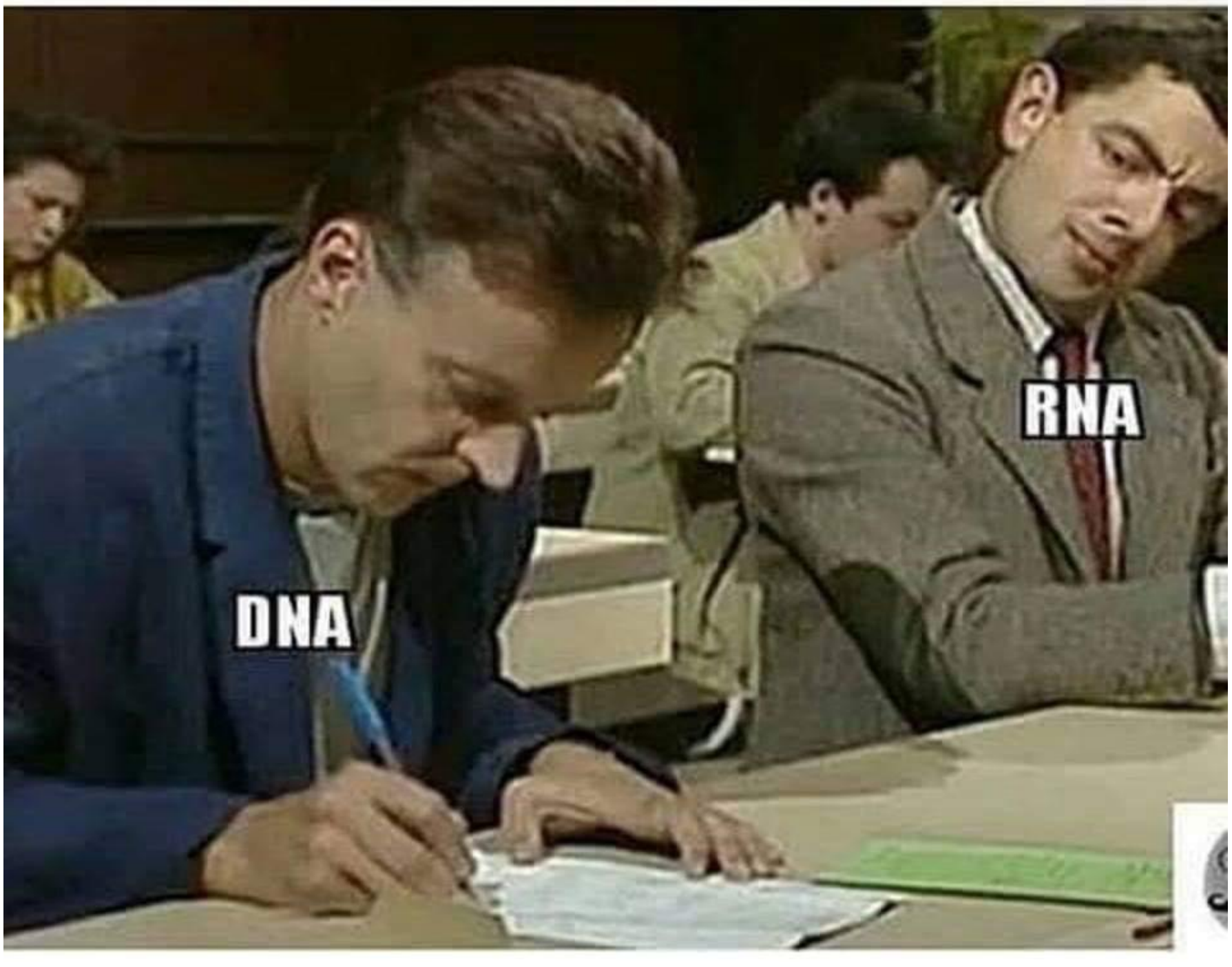
Exome / transcriptome analysis and Target Discovery & Validation



Delivery systems, generate mAbs protein engineering



Tailor-made the appropriate nano-vehicle, selective targeting agent and specific therapeutic payload

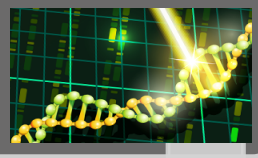

DNA
RNA

The medicine of the future

Sequence patients with a particular disease (e.g. Cancer)

Learn about the mutations and genes that are overexpressed

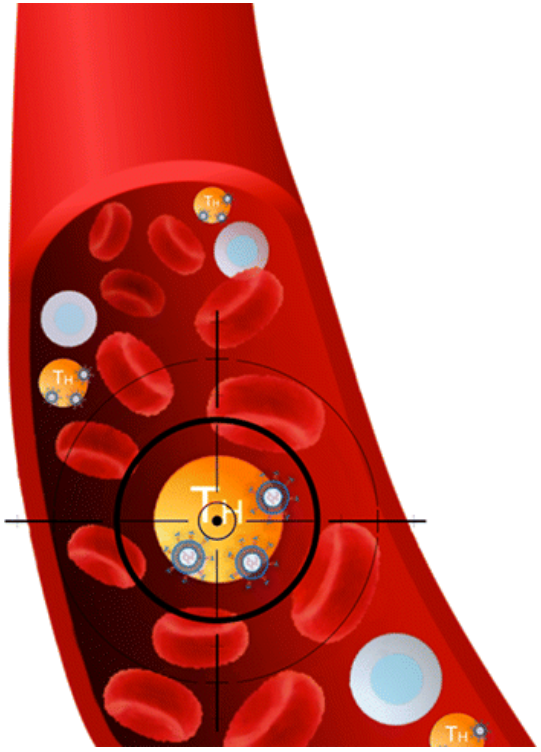
Design and synthesis new drugs based on RNA that fits the patient profile



Design and synthesis of new delivery systems that can carry RNA molecules

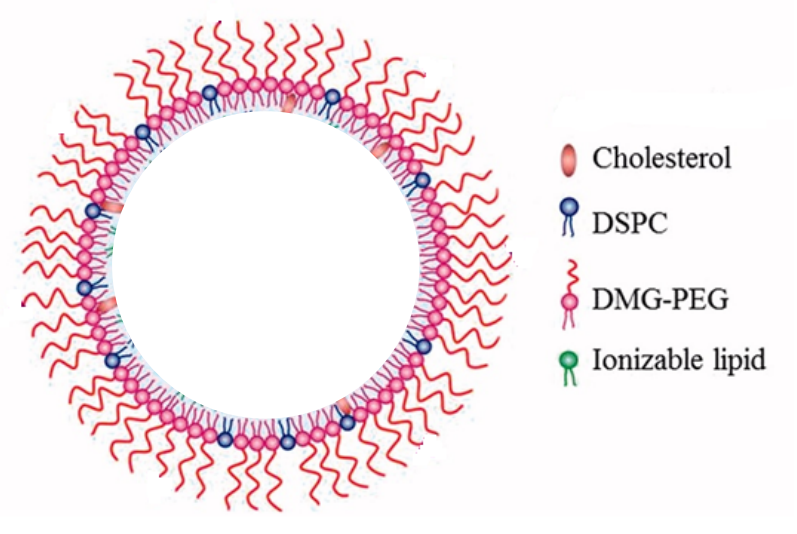
1994: ~1B$/ one human genome
2018:~800$/ one human genome

Targeted Nanoparticles



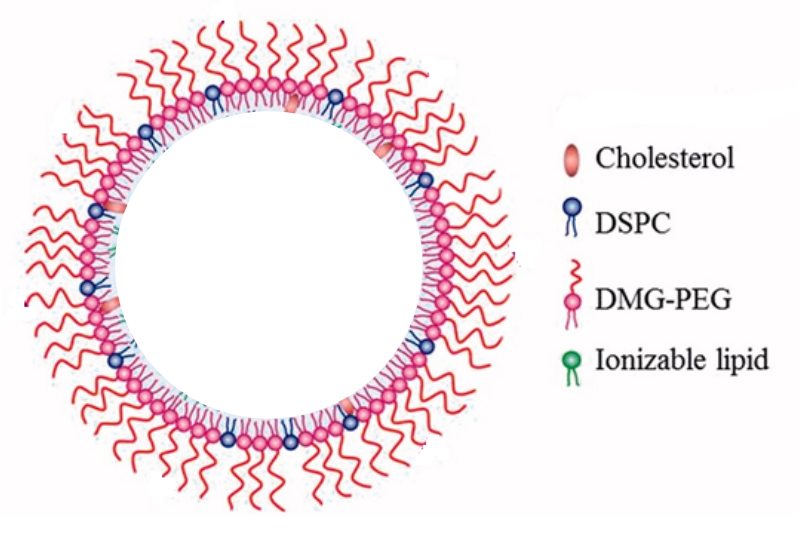
Targeted lipid nanoparticles

- Components:
  - Carrier: that can package the drug



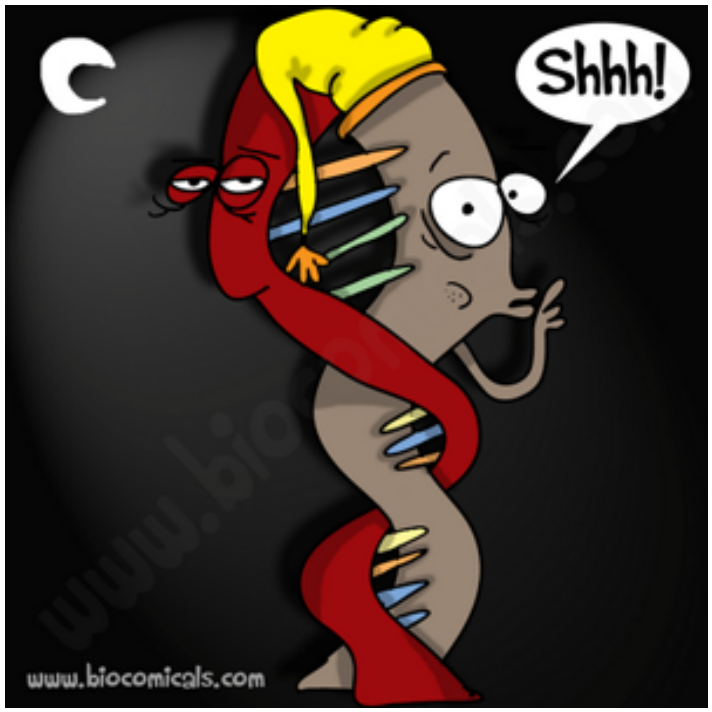
Targeted lipid nanoparticles

- Components:
  - Carrier: that can package the drug
  - Drug: RNA sequence (siRNA or mRNA)



The drug-nucleic acid

siRNA



mRNA

RNA delivery carriers: requirements for leukocytes – an extra challenge

Efficient RNA encapsulation

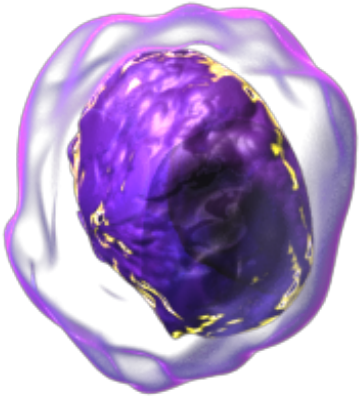
Specificity - Targeted Delivery Platform

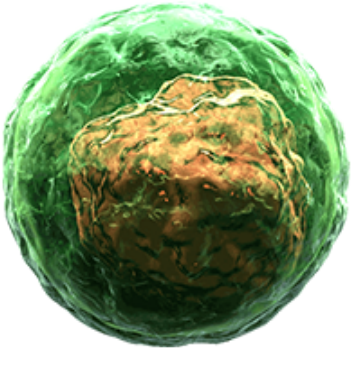
Evading clearance mechanism

Avoid toxicity and immune activation

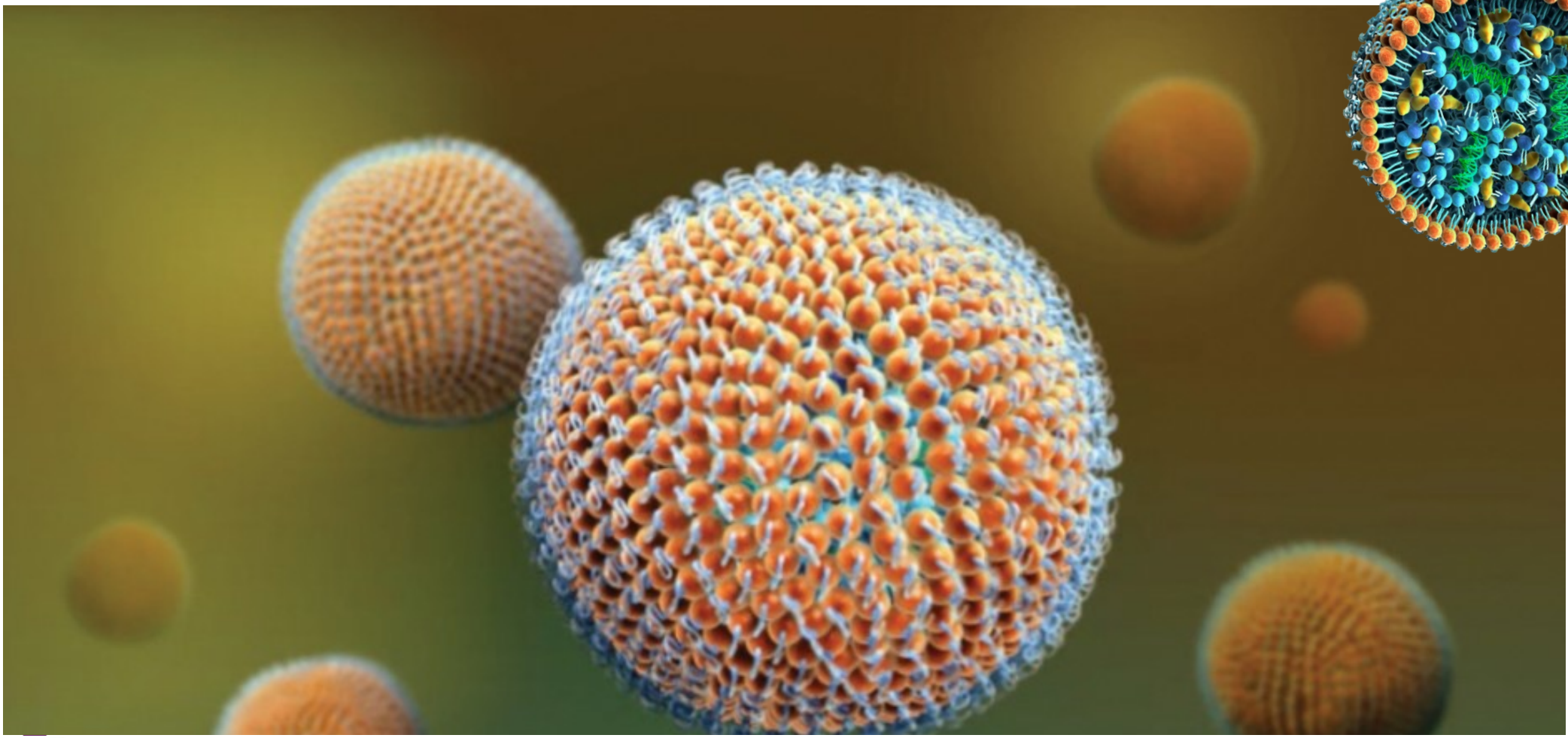
Carrier internalization

RNAi endosomal release



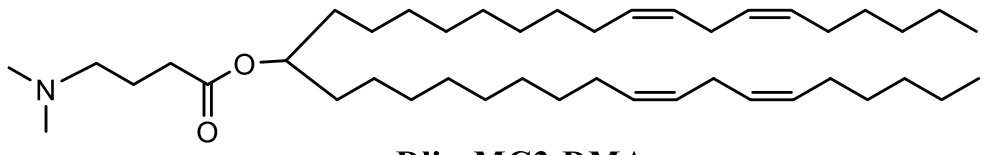


Nucleic Acid Loaded LNPs



Alnylam PHARMACEUTICALS		HUMAN POC[1]	BREAKTHROUGH DESIGNATION	EARLY STAGE *(IND or CTA Filed-Phase 2)*	LATE STAGE *(Phase 2-Phase 3)*	REGISTRATION/ COMMERCIAL[2]	COMMERCIAL RIGHTS
Patisiran	*Hereditary ATTR Amyloidosis*	✓	✓			●	Global

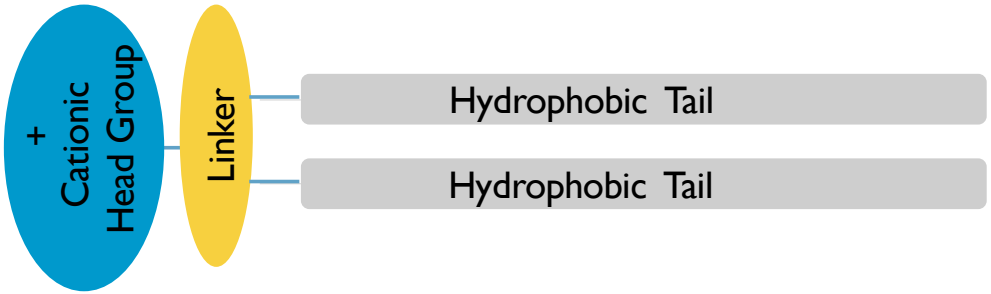
Structural design of cationic lipids



Dlin-MC3-DMA

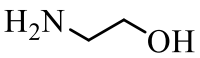
Based on the gold standard we have synthesize 60 lipid families

BIONTECH



NH_2-NH_2

NH_2-OH

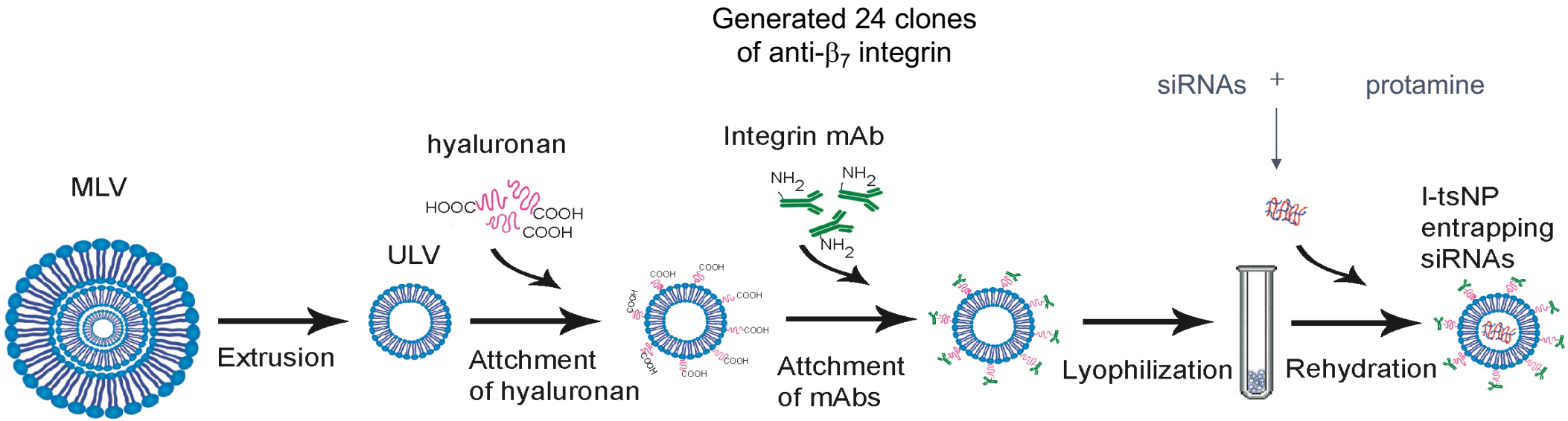


Linkers

Clinical trials

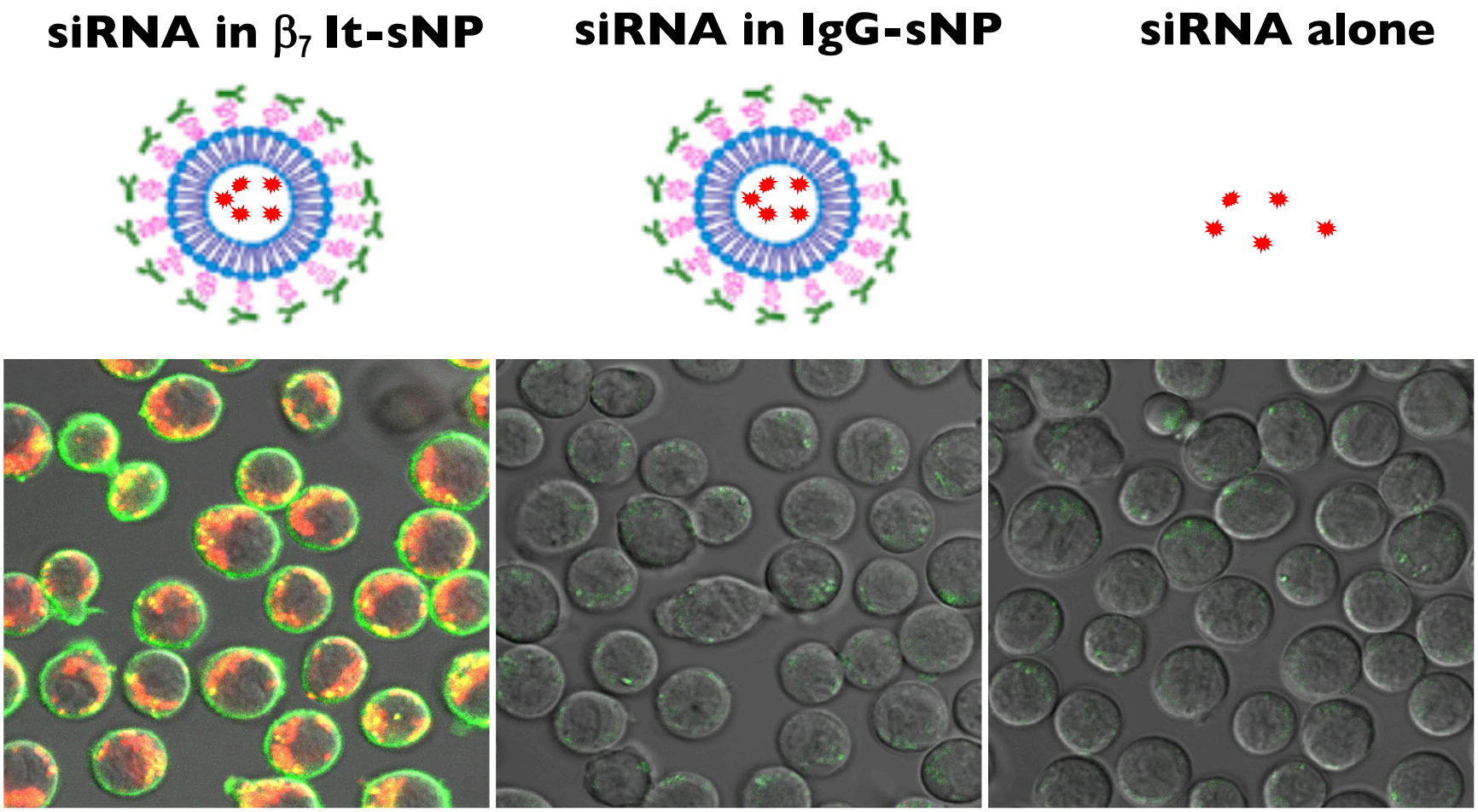
- 250 trials with mRNA (neoantigens; personalized; immuno-therapy – cytokines; PD-1 and combinations
- 50 with siRNAs (silencing genes)
- 40 with Genome Editing approaches

Systemic RNAi strategy to manipulate leukocytes' function *in vivo.*



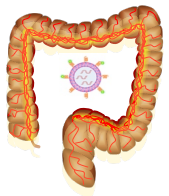
SCIENCE , 2008, **319**, 627-630

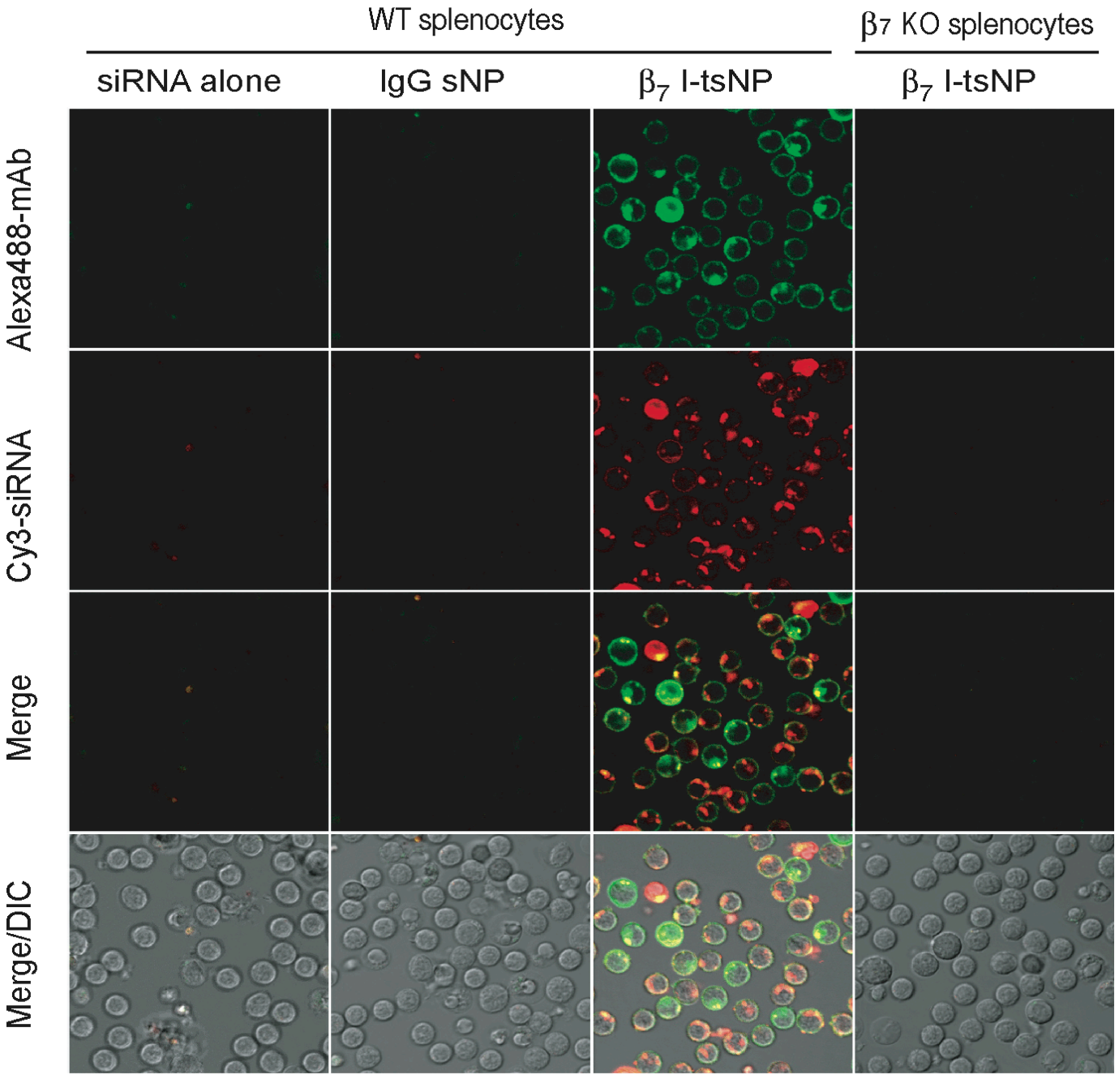
β_7 l-tsNP delivers siRNA intracellularly in lymphocytes

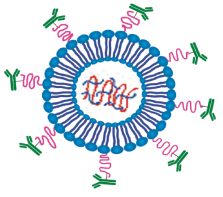


SCIENCE , 2008**, 319**, 627-630

β_7 I-tsNP delivers siRNA selectively to β_7 integrin$^+$ cells

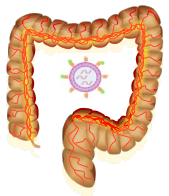




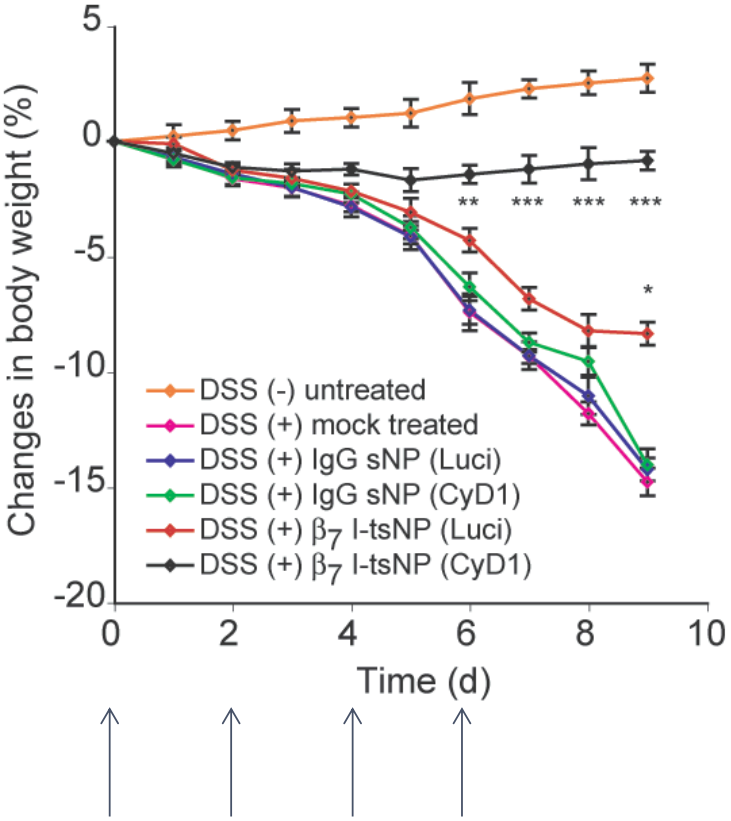


SCIENCE , 2008, **319**, 627-630

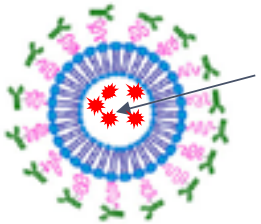
siCyD1 delivery with β_7 I-tsNP alleviates gut inflammation in DSS-induced colitis. CyD1 as an anti-inflammatory target is now a new drug target for inflammatory bowel diseases.



Body weight changes

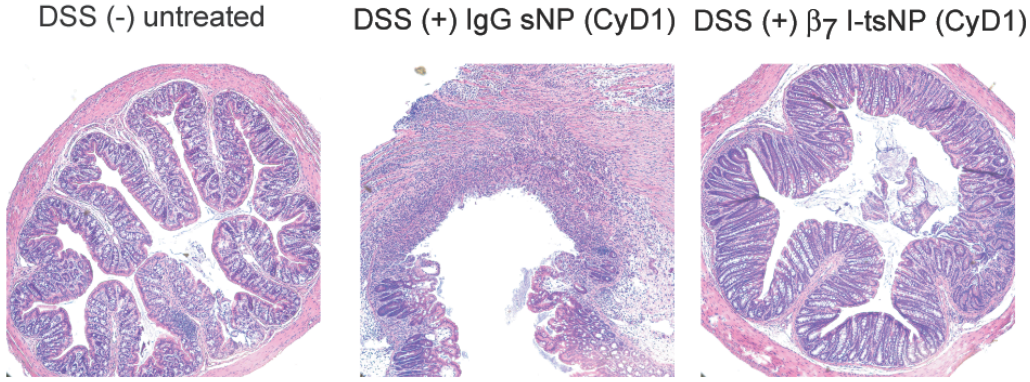


β_7 I-tsNP



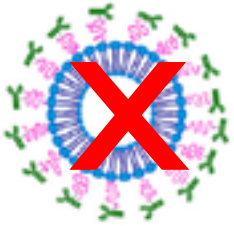
siCyD1

Gut histology

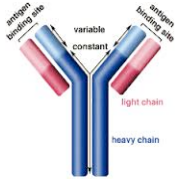


Science 2008, **319,** 627-630
Alberts, Molecular Biology of the Cell, 6th edition and beyond

Licensing



Genentech
IN BUSINESS FOR LIFE

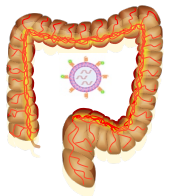


Clinical Translation (anti-β7 mAb) Etrolizumab

FIH Aug. 2010: 35 patients (safety and escalating doses)
Phase IIa randomized double blinded :
Oct. 2012 :61 patients – moderate-to-severe CD
Phase IIb - randomized double blinded: Dec. 2013:223 patients moderate-to-severe CD
Phase III - randomized double blinded : Dec. 2014 – April 2017: overall 923 patients
Interim results (500 patients): Dec. 1st, 2016 published
Pre-marketing approval: August 2018
In addition: 4 phase III clinical studies are progressing towards the end (mid and end of 2020).

Genentech
A Member of the Roche Group

Global conformational changes of integrins



PNAS , 2006
PNAS, 2007
Nature Nanotech, 2007
Immuno Rev. 2013
ACS Nano 2013
ACS Nano 2015
Lancet 2015
Immunity 2016
Front. Immuno. 2017
ACS Nano 2017
Nature Nanotech. 2018
Nature Comm. 2018

Vedolizumab

Etrolizumab

Genentech
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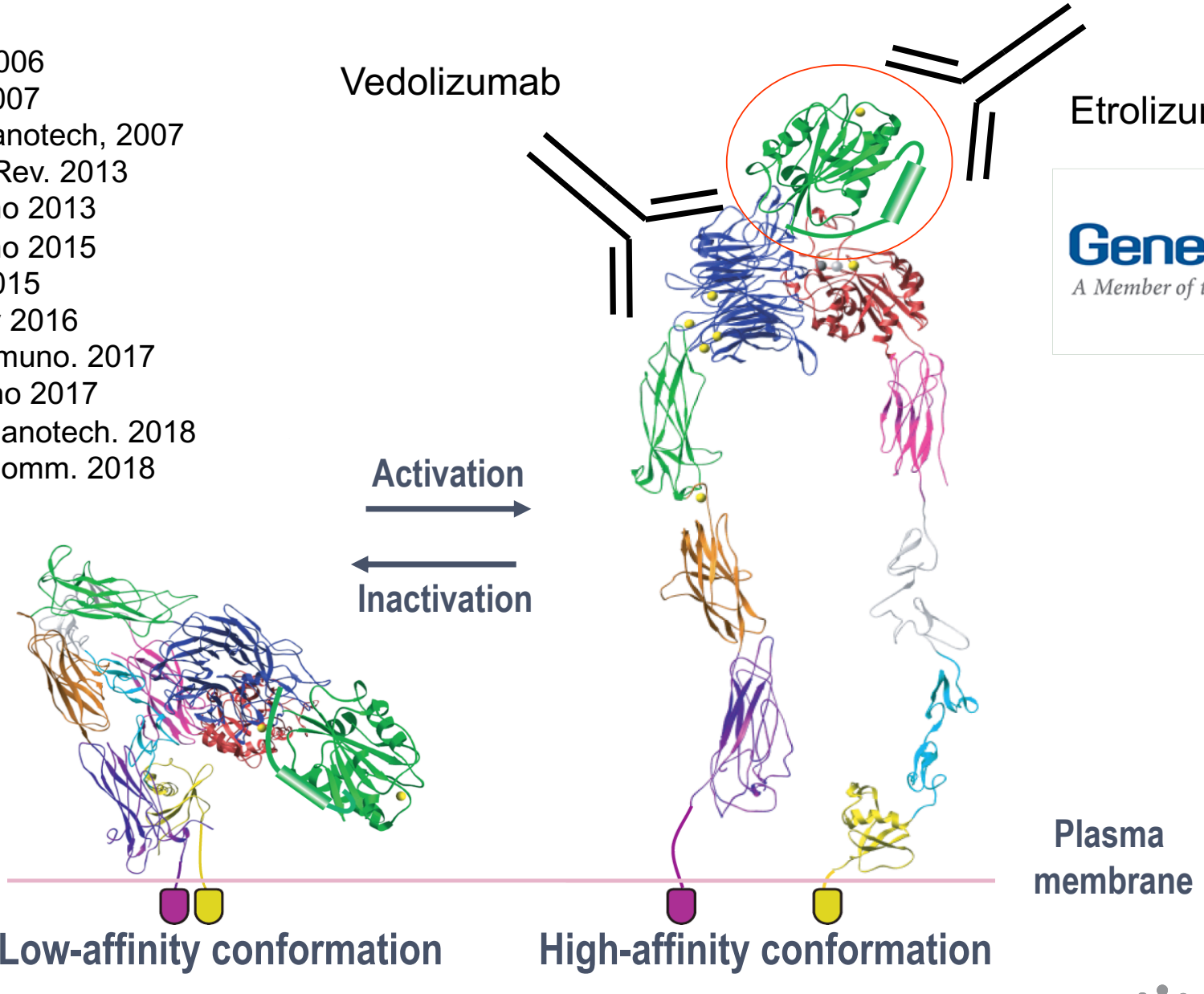
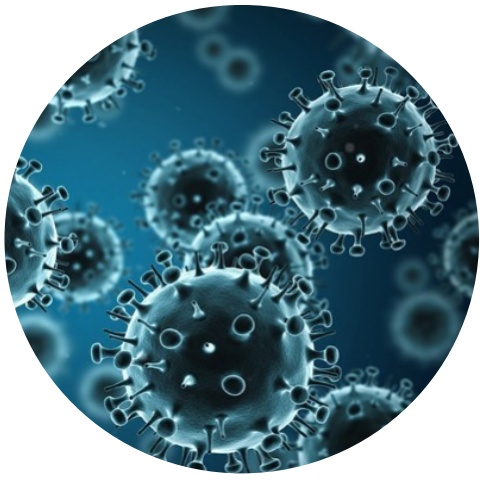
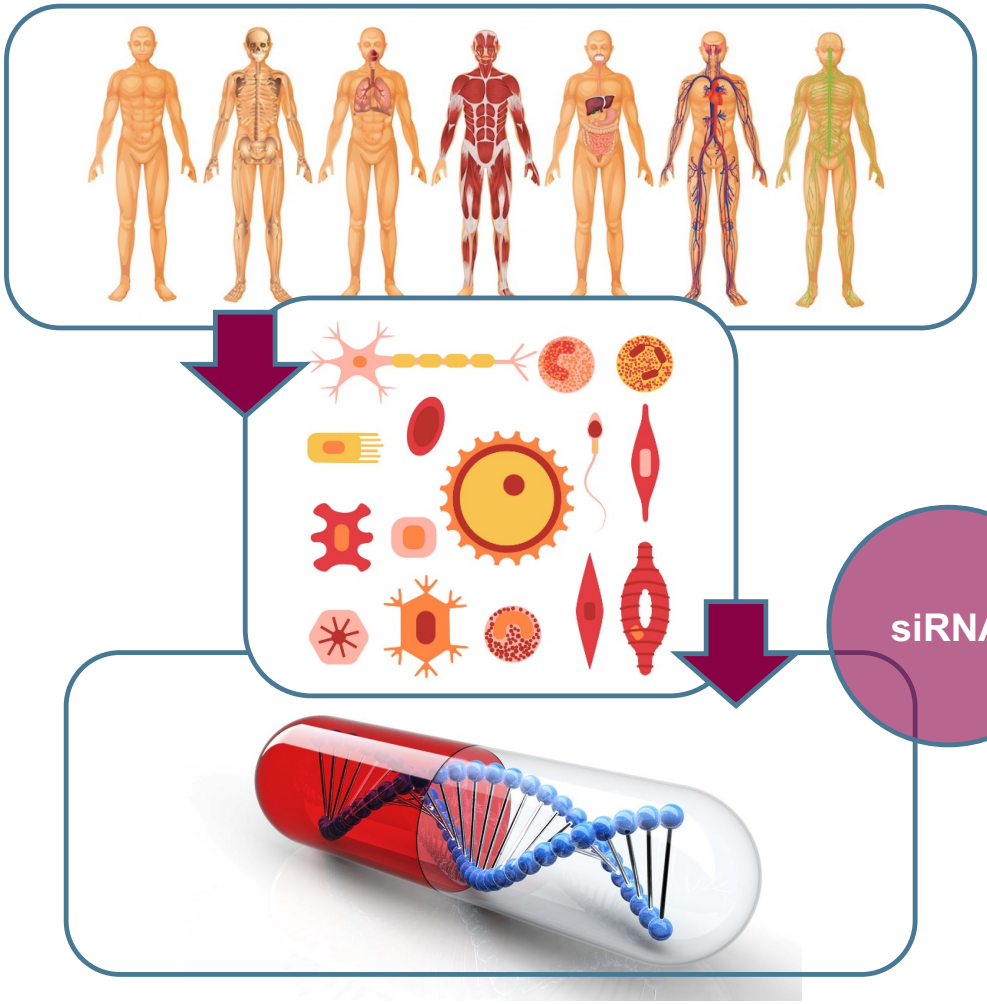


Human Diseases Heterogeneity

NIH
NHGRI

The Complexity of Human Disorders



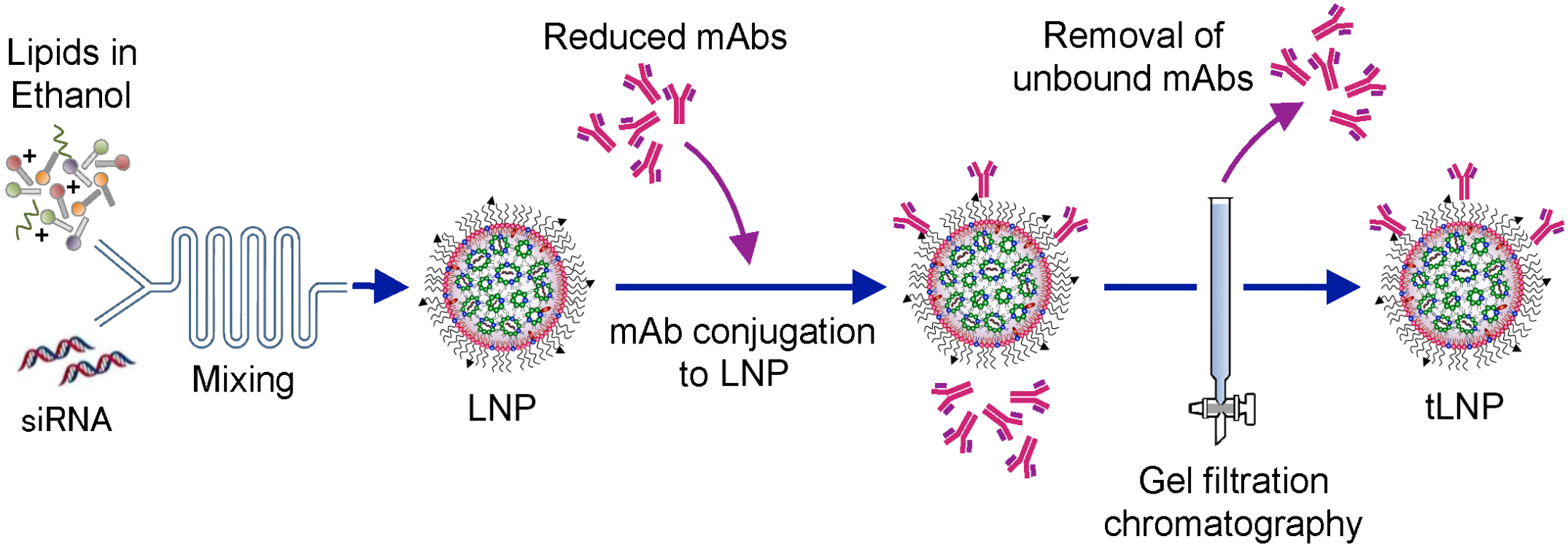


siRNA

saRNA

mRNA

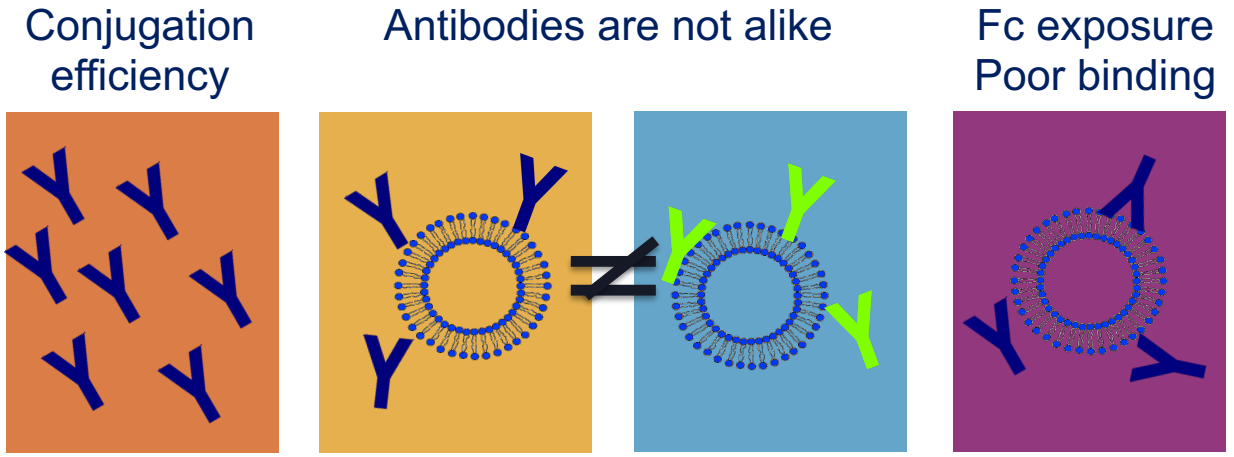
Streamline the production of targeted RNAi nanomedicine



Mizrahy S. et al. Molecular Therapy 2017

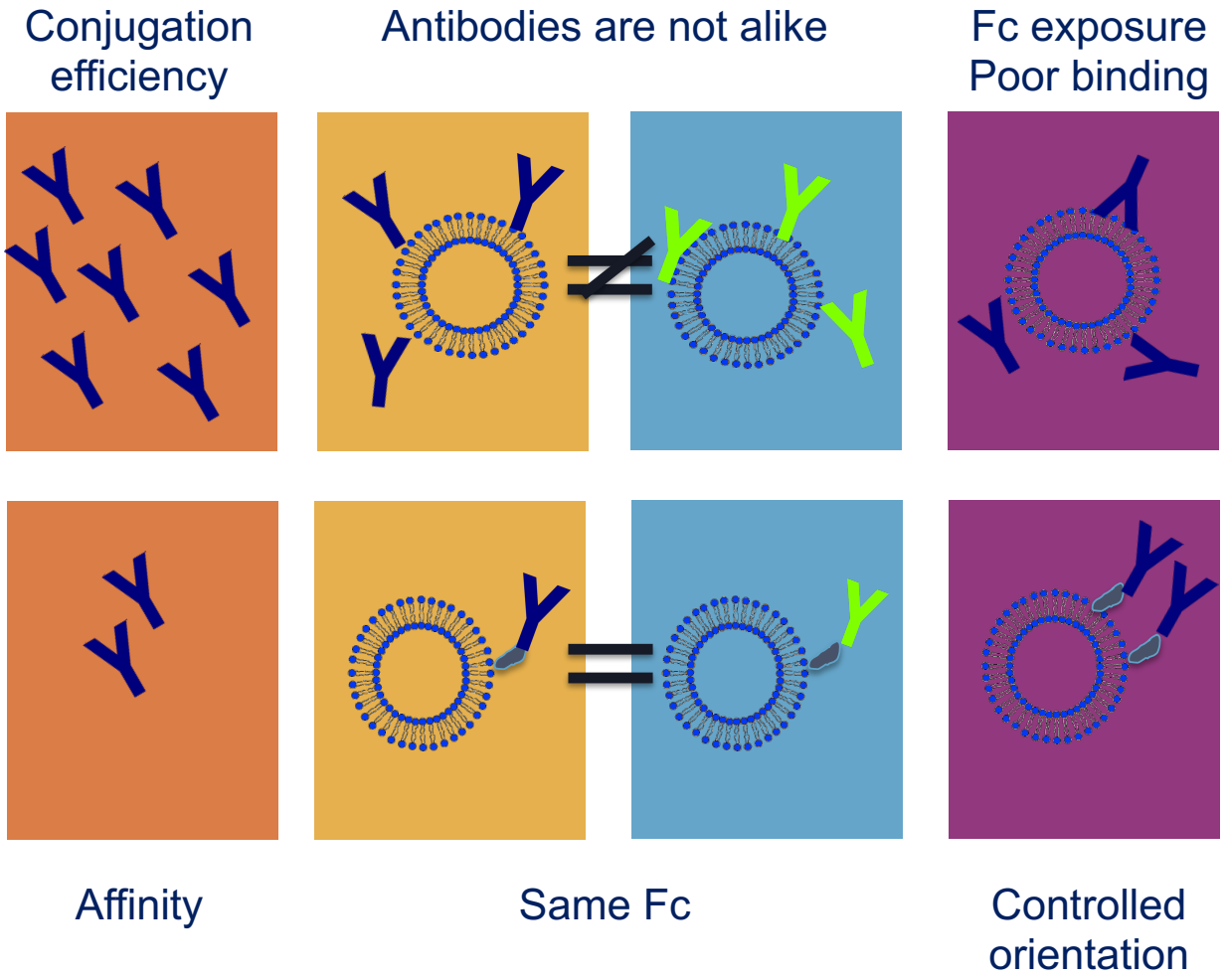
tLNPs construction drawbacks

Chemical Conjugation



tLNPs construction drawbacks

Linker strategy



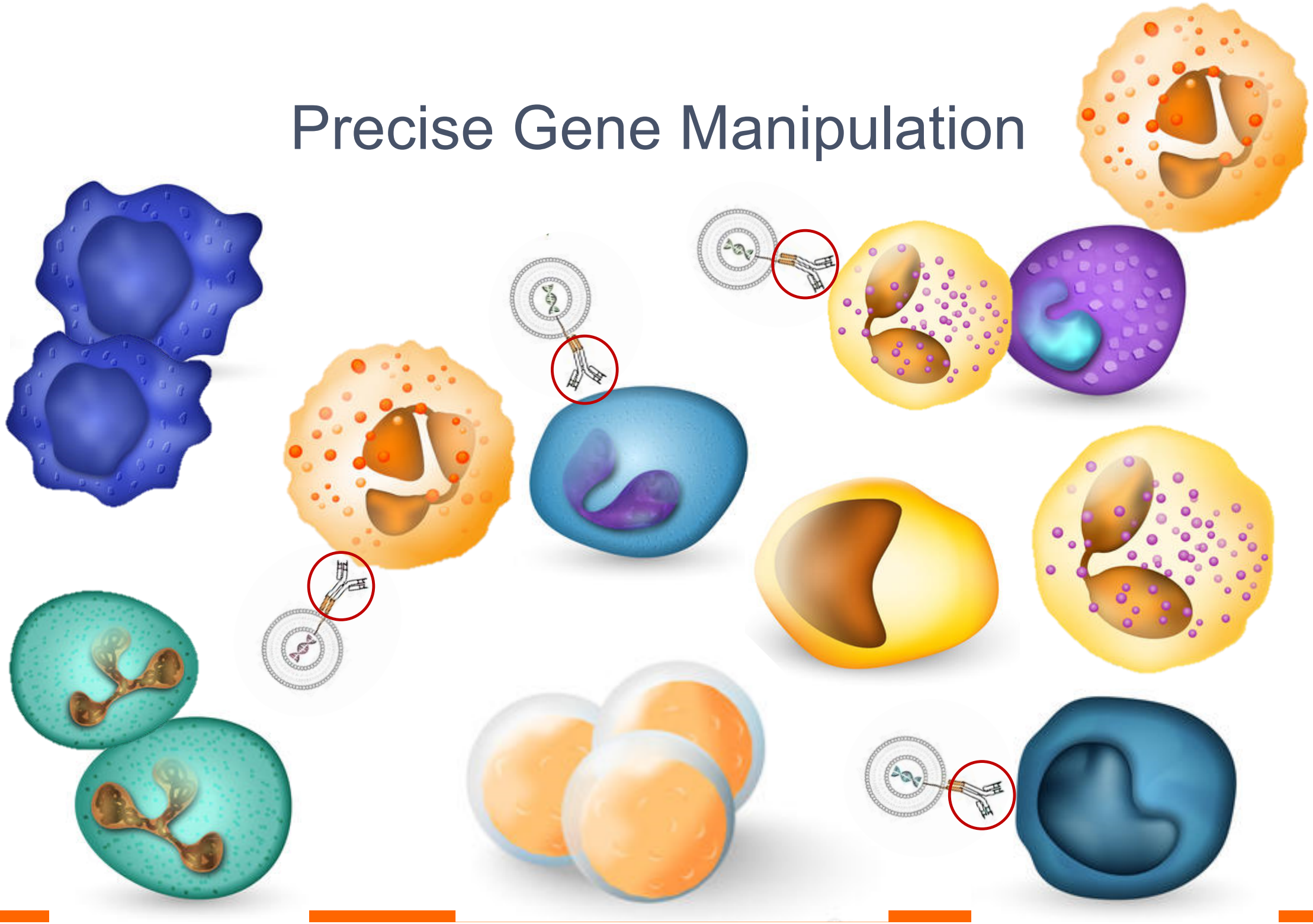
Linker strategy

Affinity Versus Chemical Conjugation

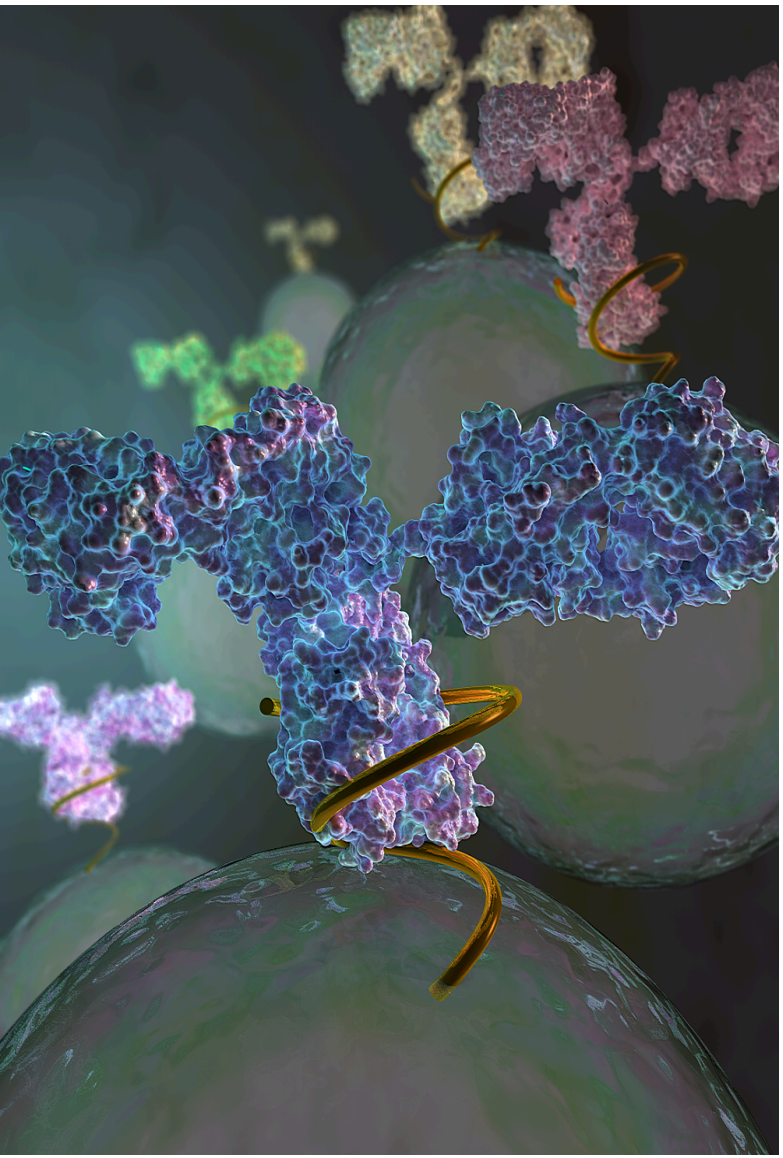
Ranit Kedmi, Ph.D.

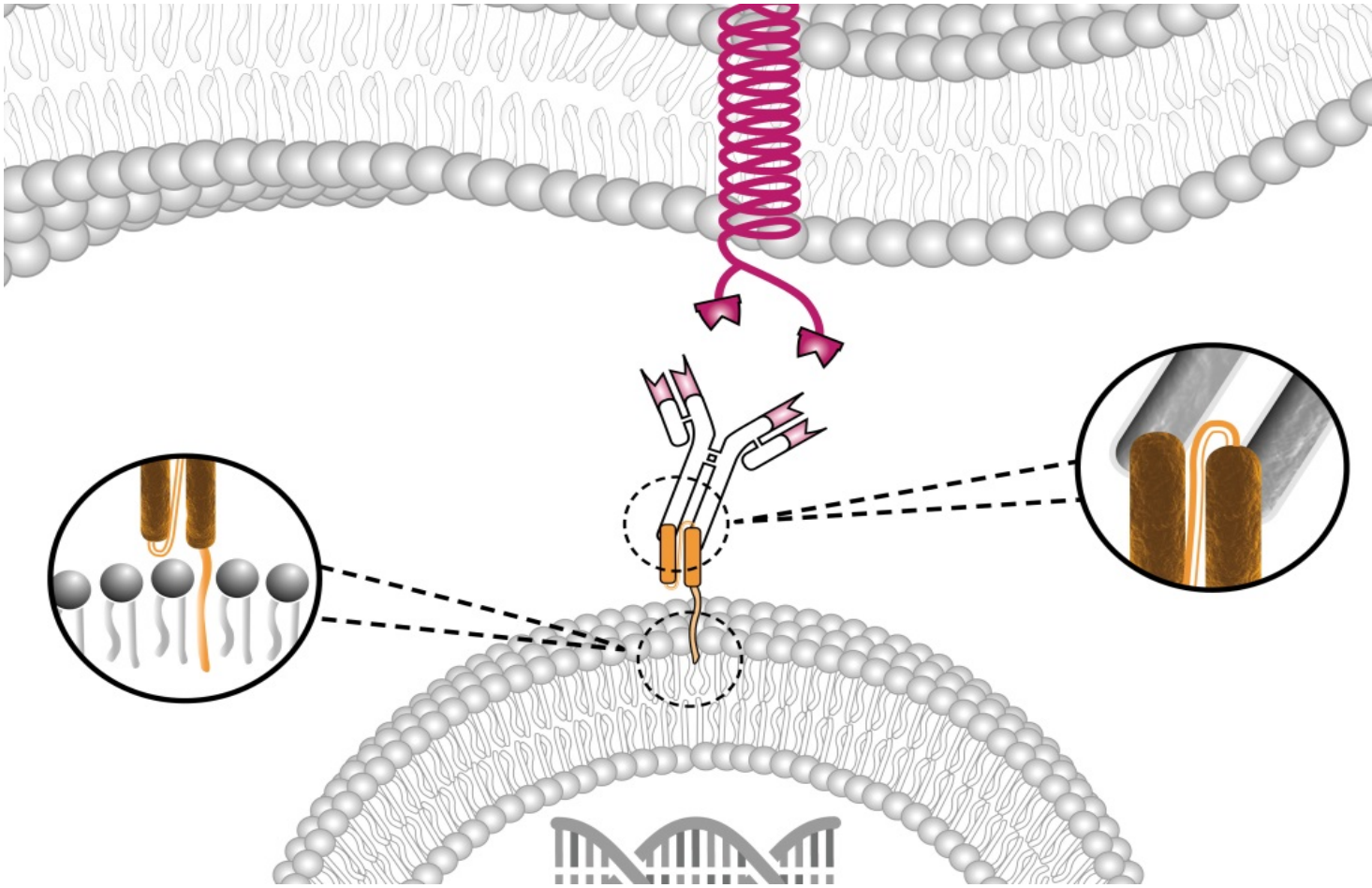
Nuphar Veiga, Ph.D.

Precise Gene Manipulation



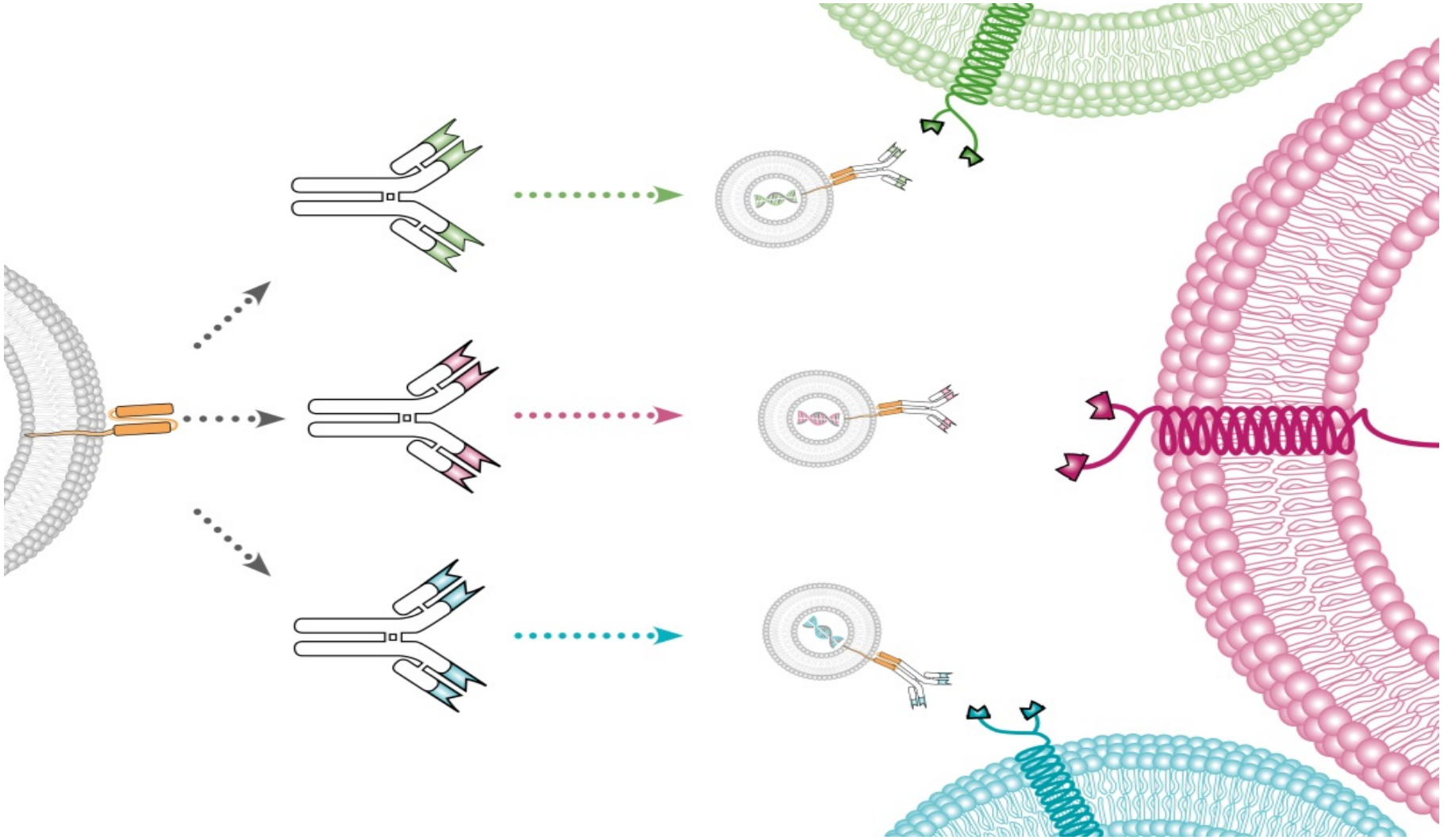
Schematic illustration of the linker strategy





Kedmi, R* and Vaiga N.* . *et.al* . Nature Nanotechlogy 2018

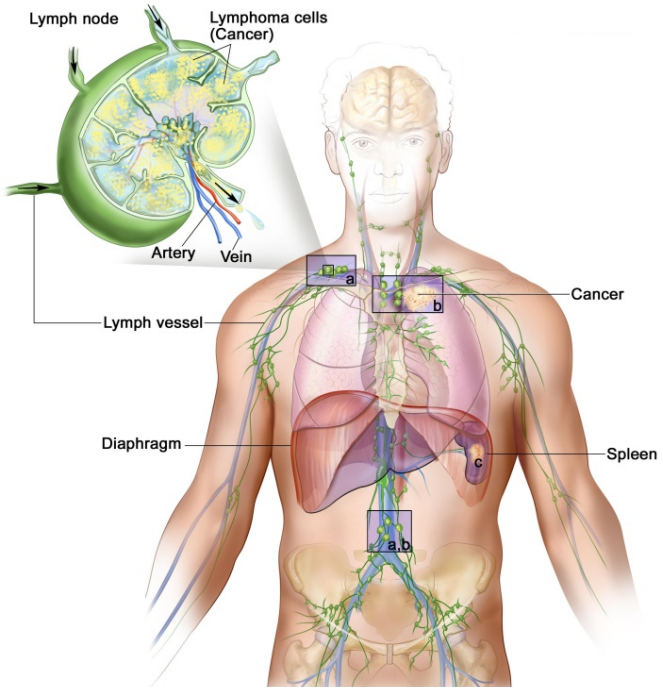
Platform Versatility



Kedmi, R* and Vaiga N.* . *et.al* . Nature Nanotechnology 2018

Therapeutic Applications

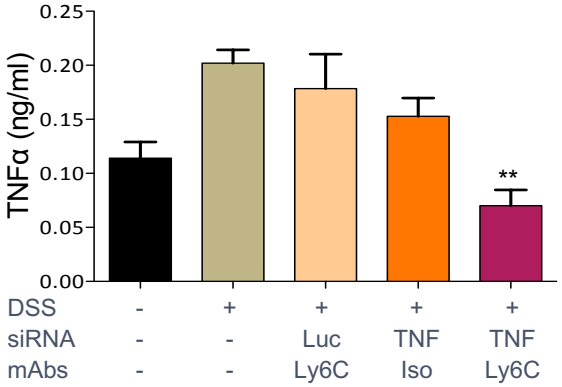
MCL

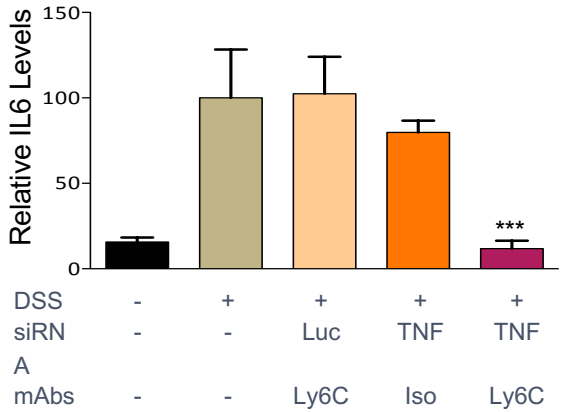


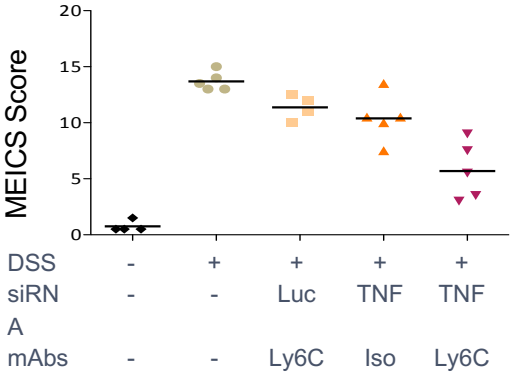
Colitis

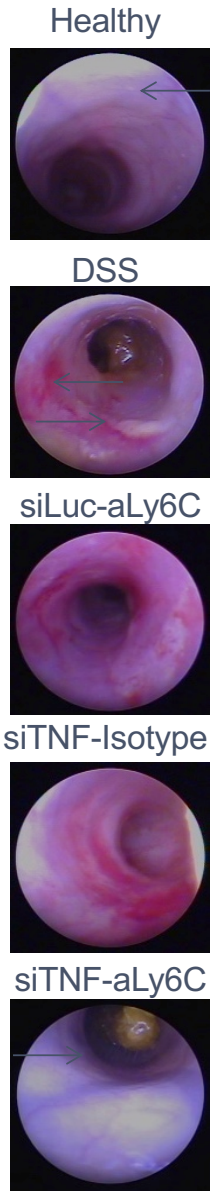
Target cells: Ly6C^{hi}
Target gene: TNFa

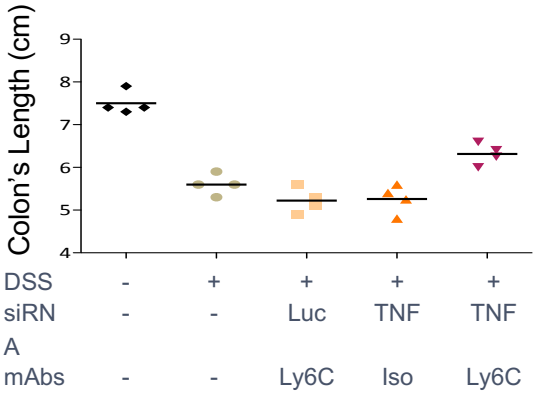
Therapeutic Effect in DSS Colitis

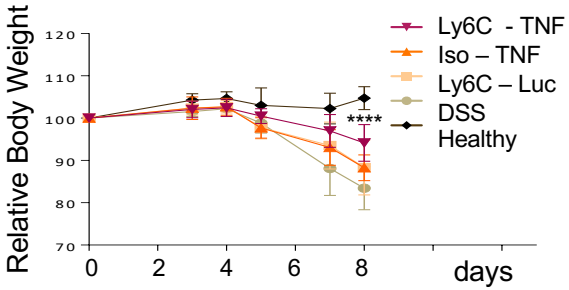








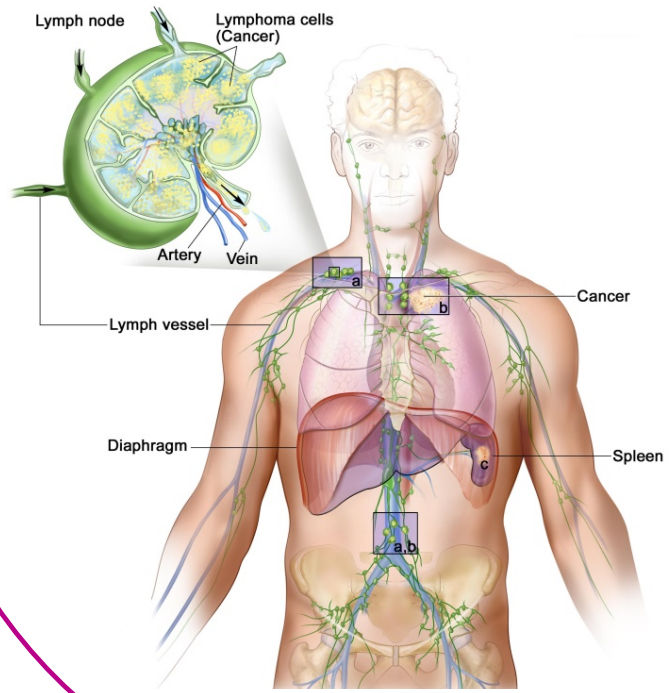




Kedmi, R and Vaiga N. . *et.al* . Nature Nanotechnology 2018

Therapeutic Applications

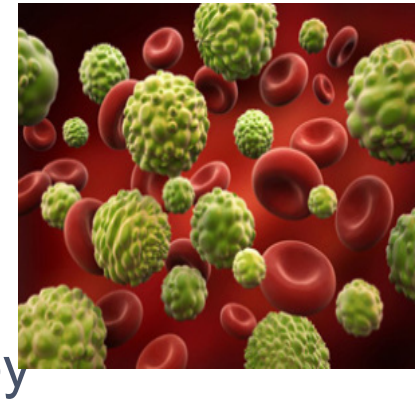
MCL

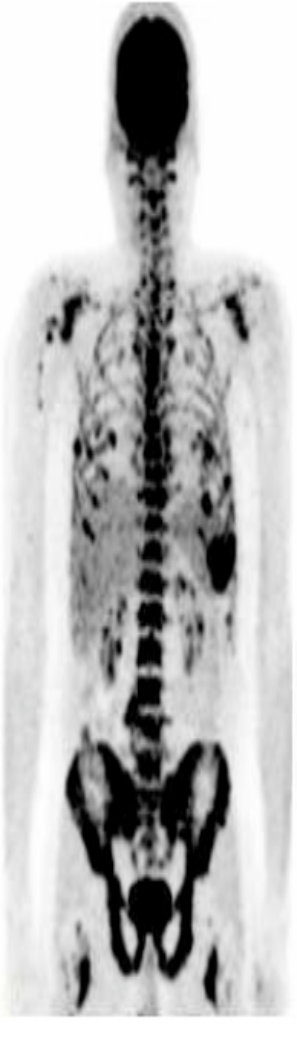


Colitis

Target cells: CD29
Target gene: PLK1

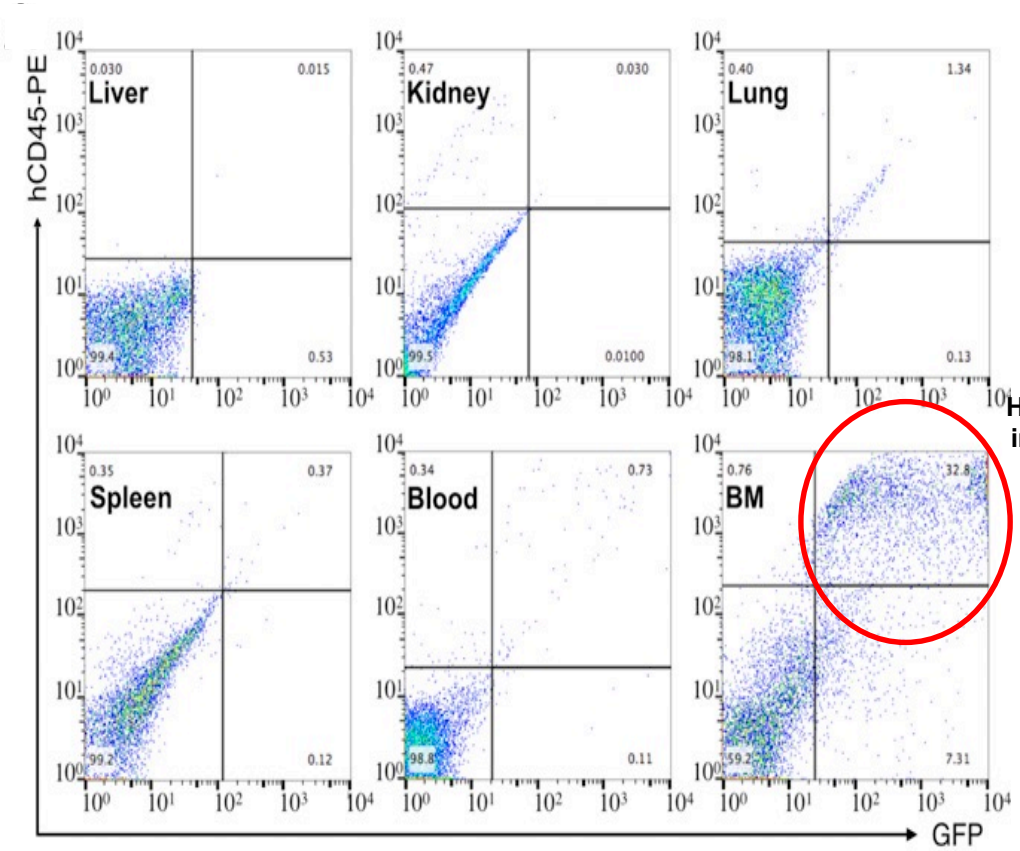
Mantle Cell Lymphoma



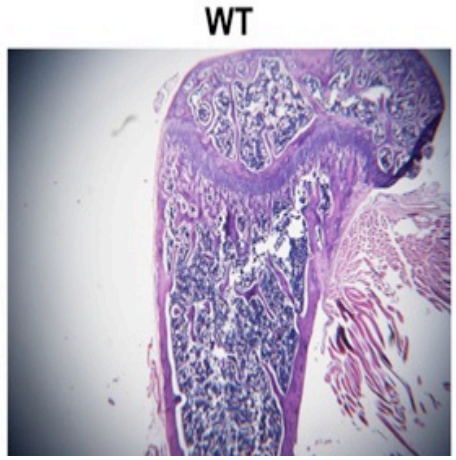


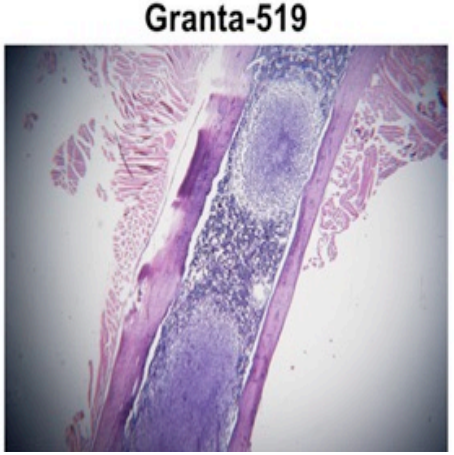
- Aggressive form of B cell non-Hodgkin lymphoma
- Relatively rare (~6% of all NHL cases)
- Considered “incurable” with traditional chemotherapy (combination of anti CD20 and chemotherapy)
- Median overall survival: 5-7 years (poorest among B cell lymphomas)

MCL-xenograft mice model



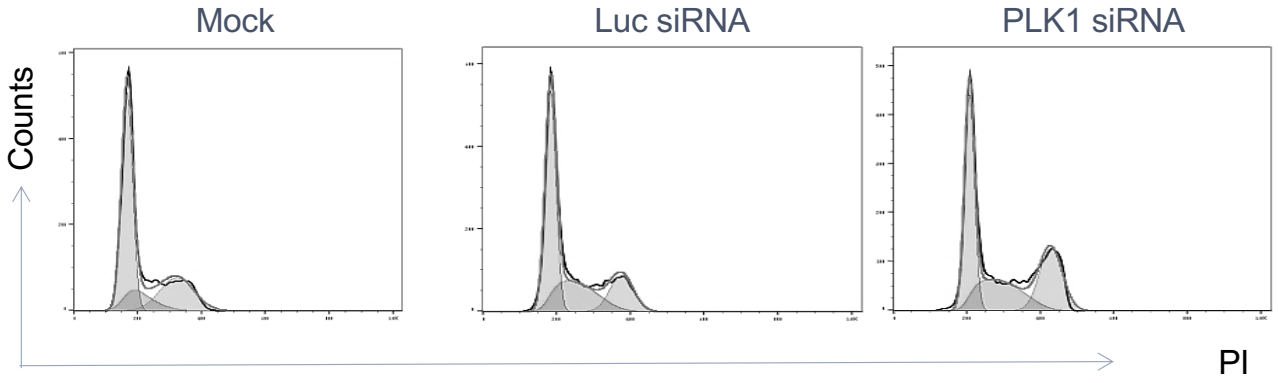
Human MCL cells in BM of injected mouse

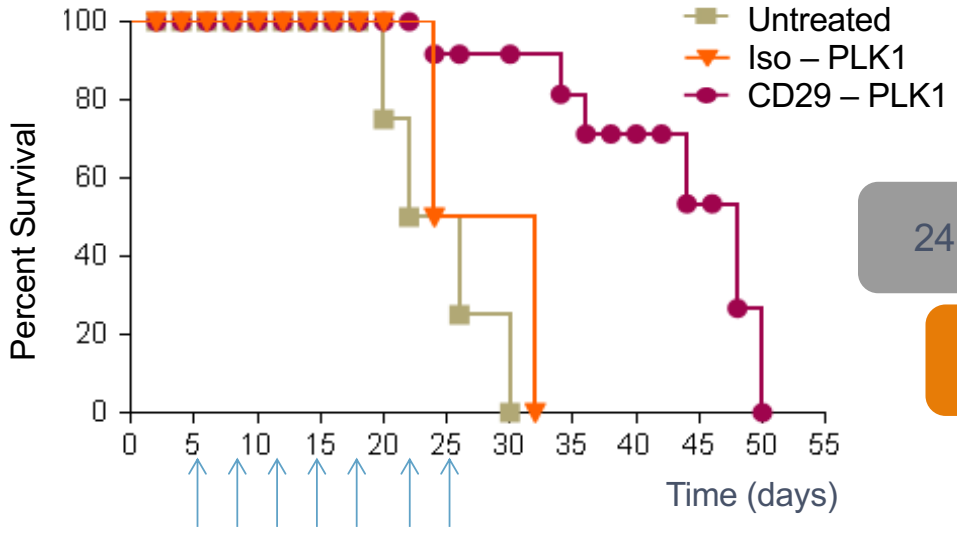




Weinstein S., Toker I. A., et al, PNAS, 2016

Prolong Survival in MCL Model





24 days Mock

28 days Iso

46 days aCD29

Kedmi, R and Vaiga N. . *et.al* . Nature Nanotechnology 2018

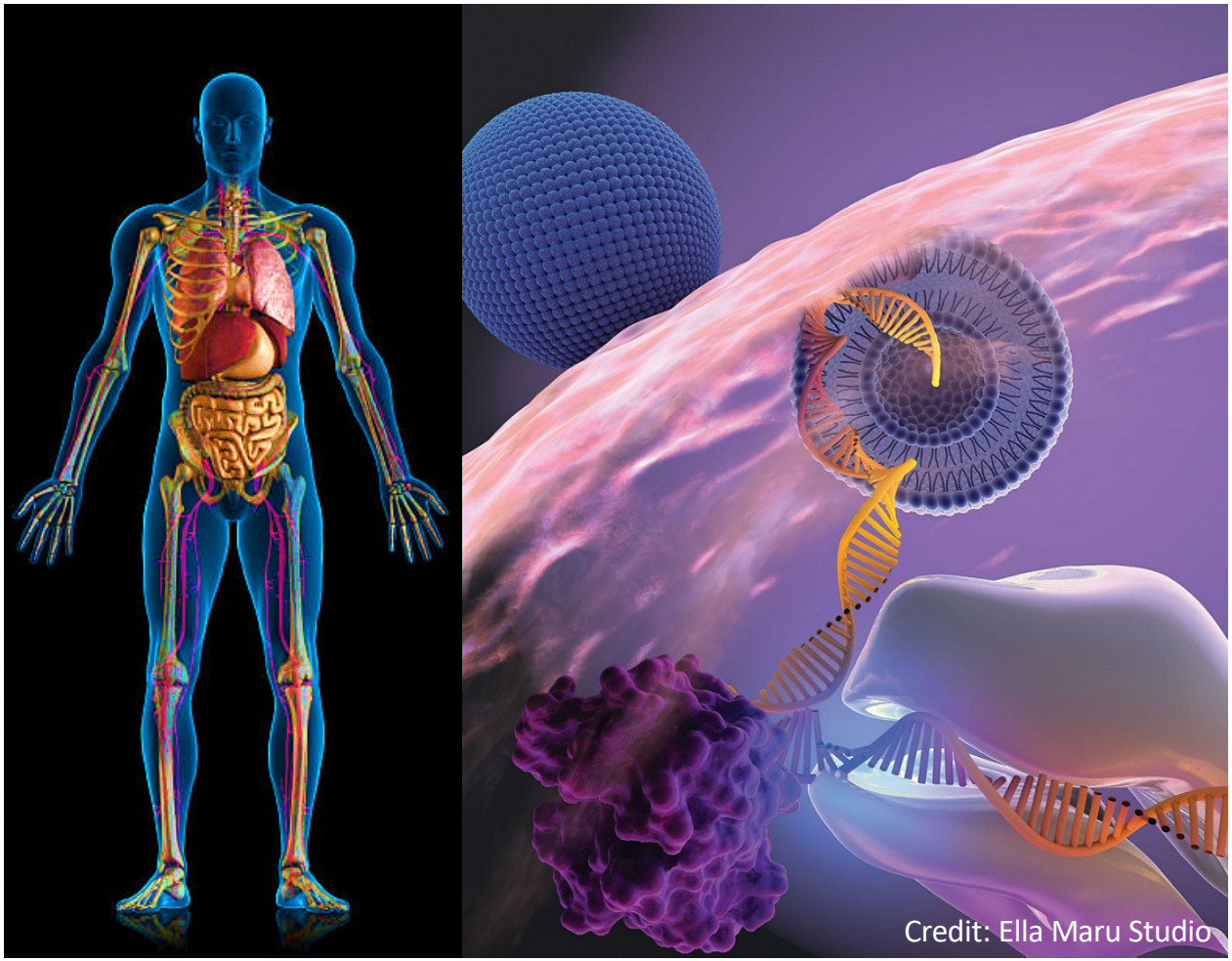
mRNA Based Therapeutic Protein Expression

Immunomodulatory proteins

Protein replacement

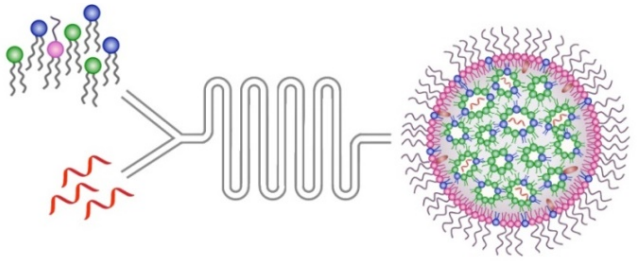
Cancer therapy

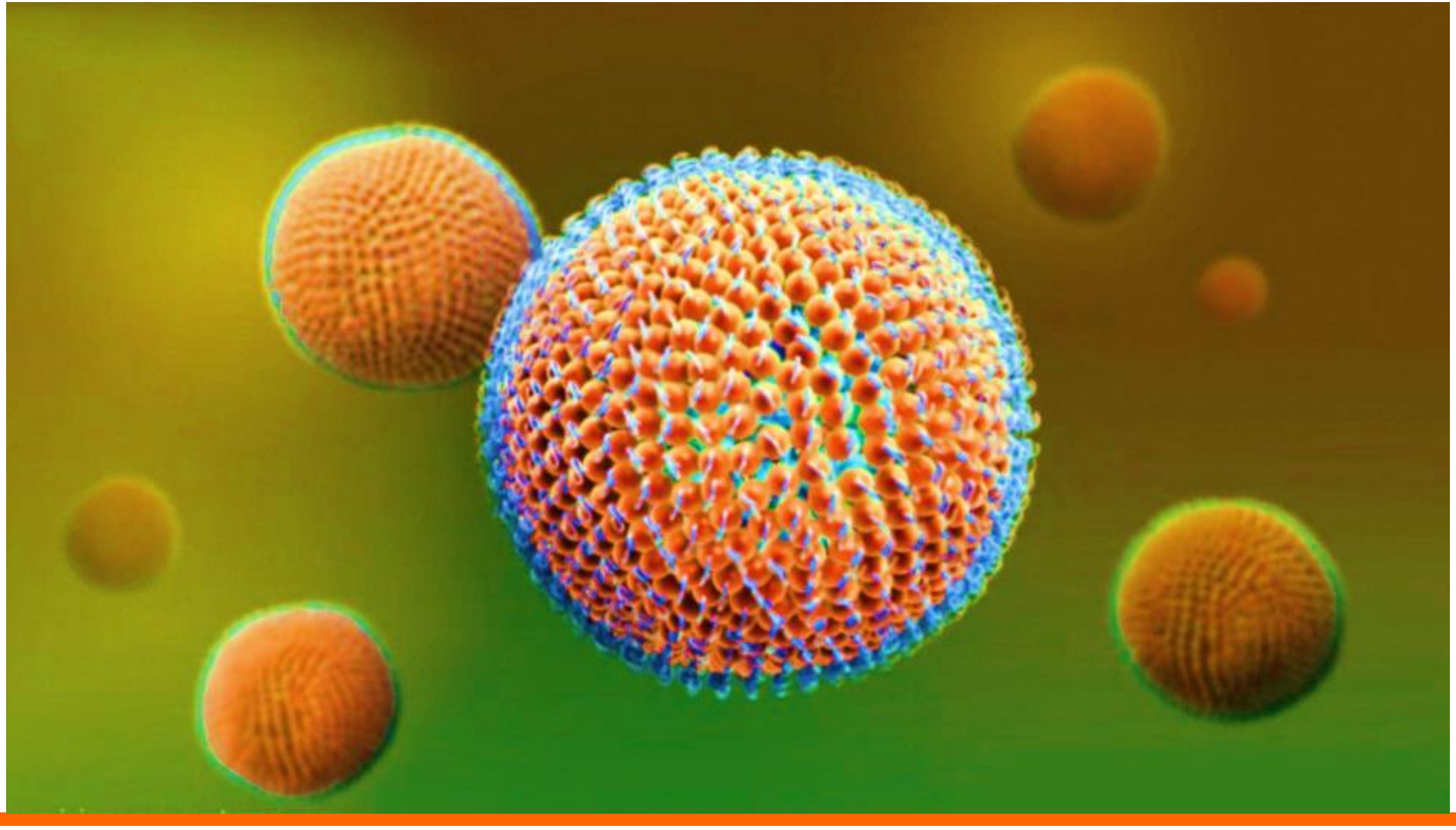
Vaccination



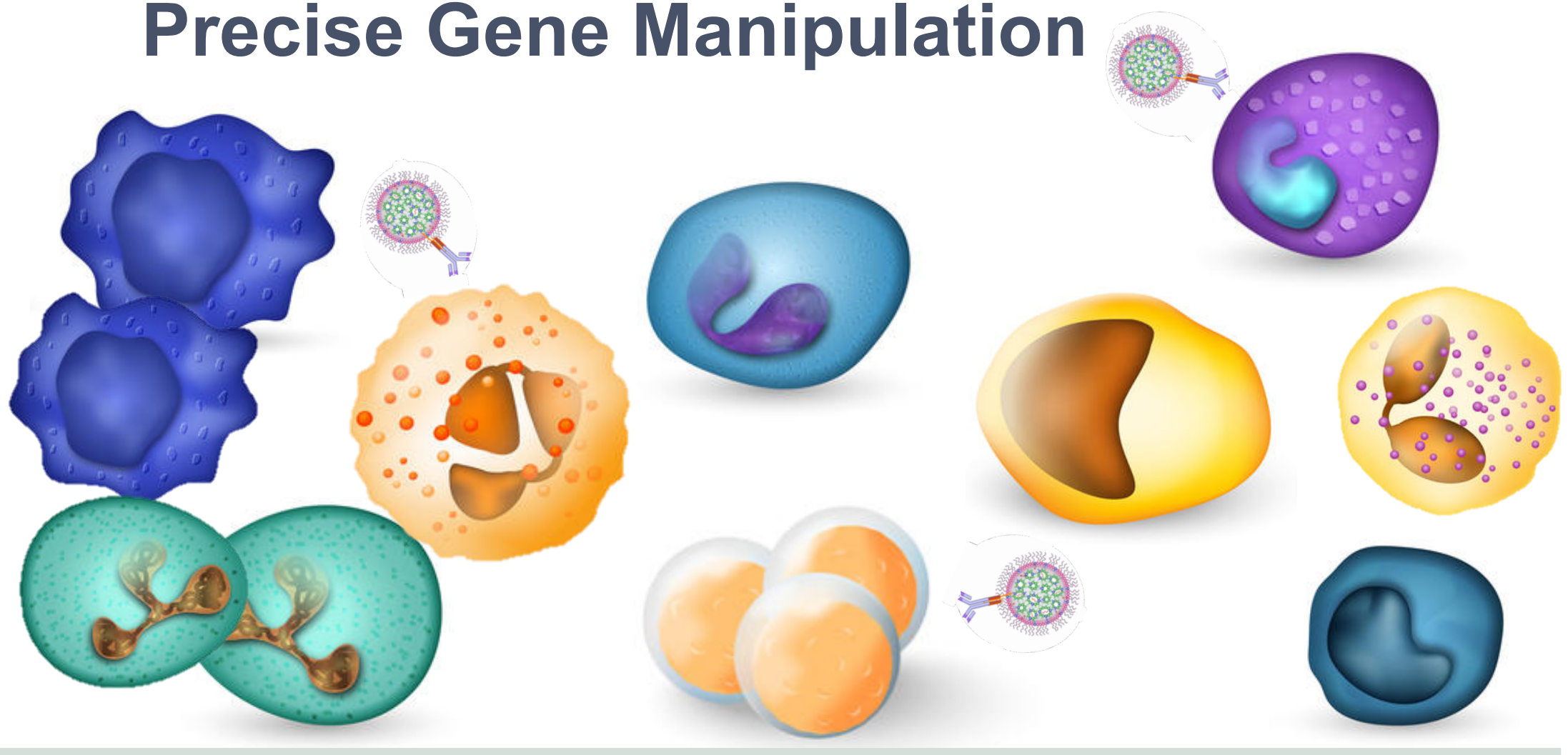
Nuphar Veiga, Ph.D.

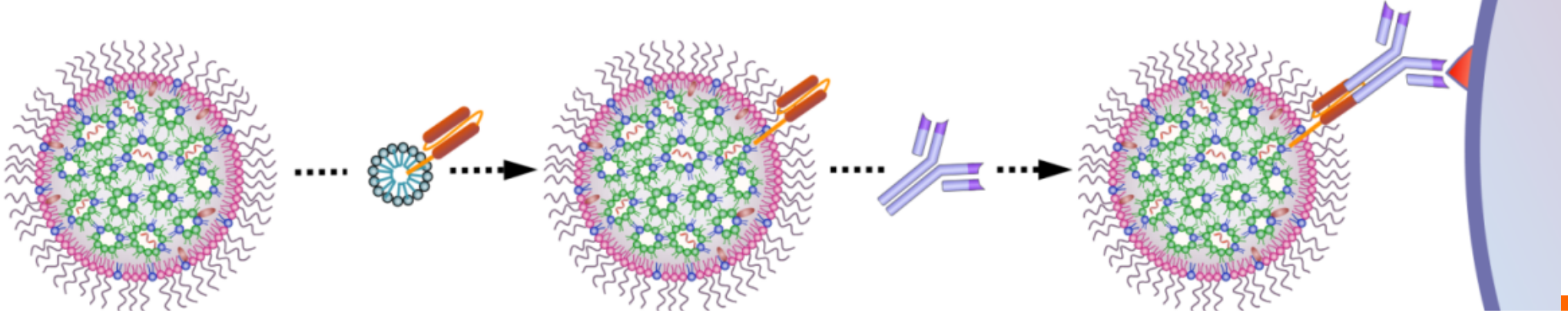
mRNA Loaded LNPs



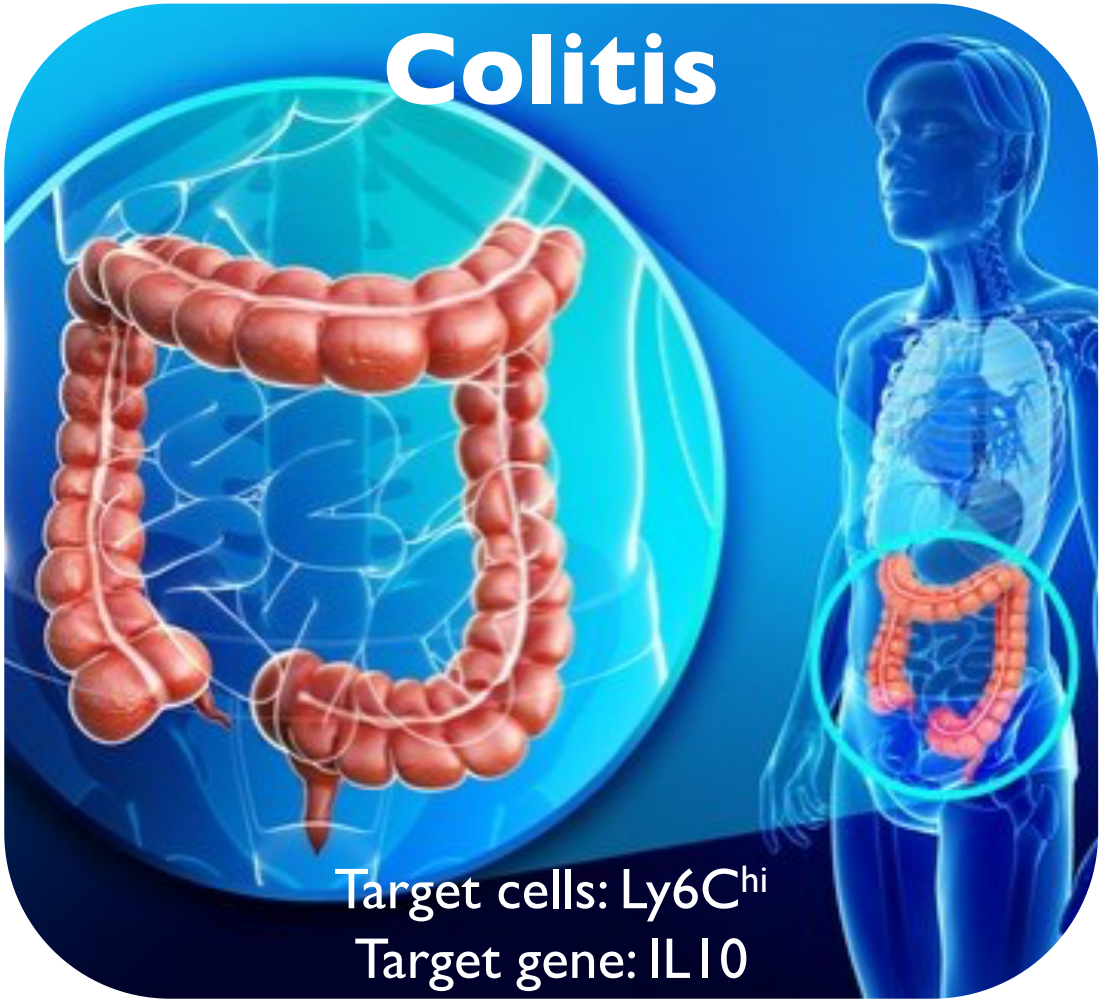


Precise Gene Manipulation



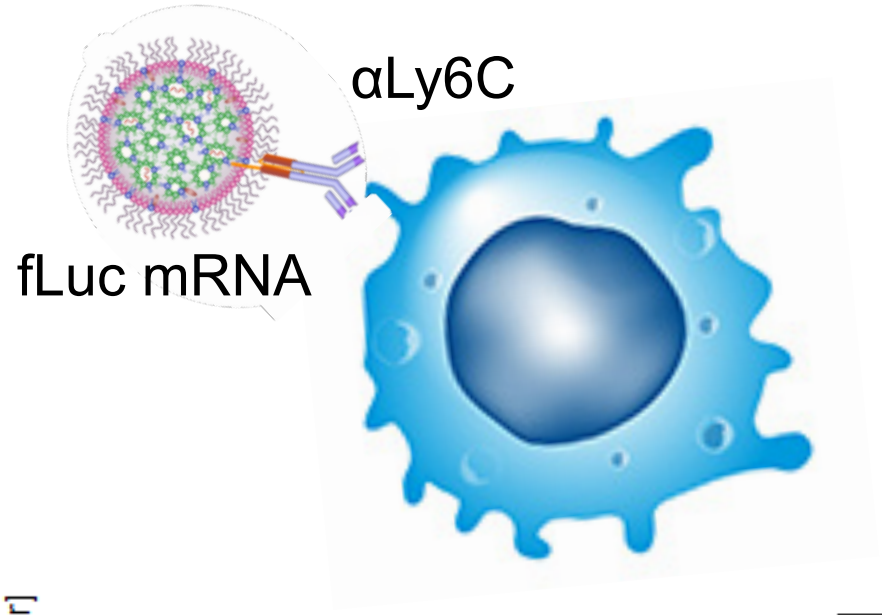


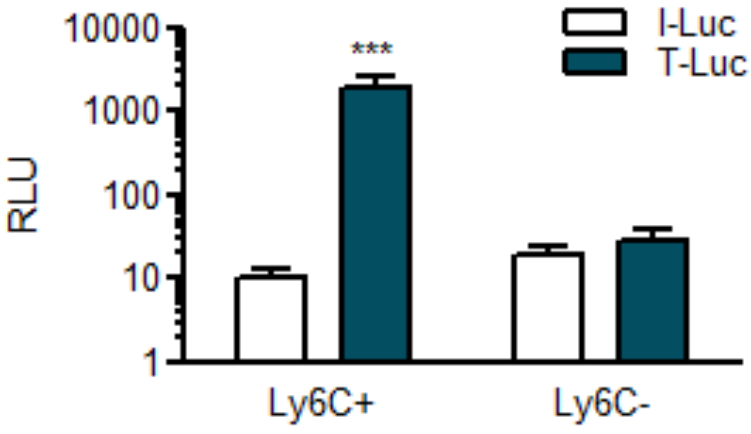
Targeted Immunomodulation

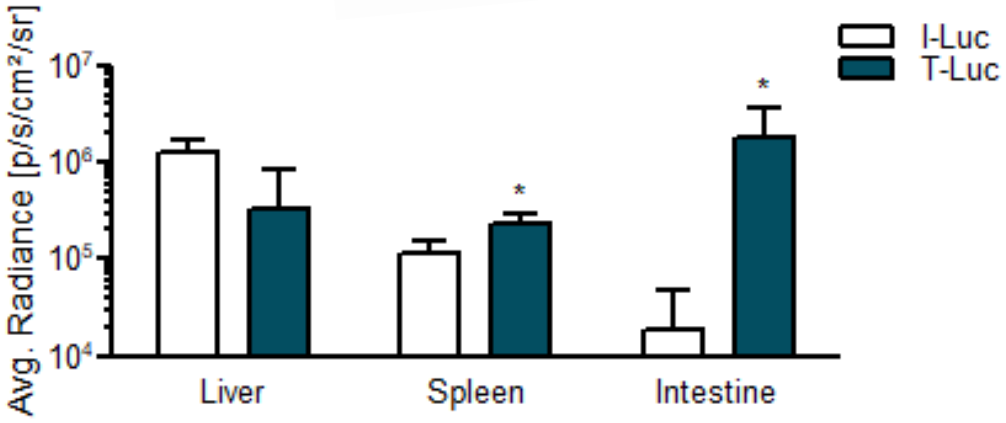


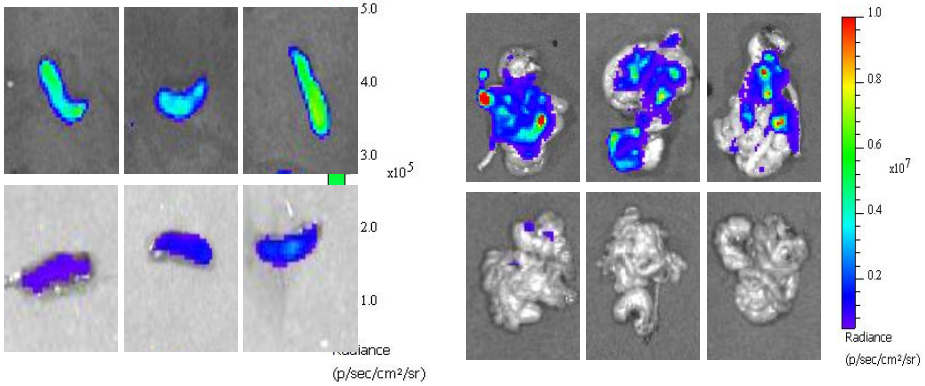
DSS model

Targeted Protein Expression *In-vivo*



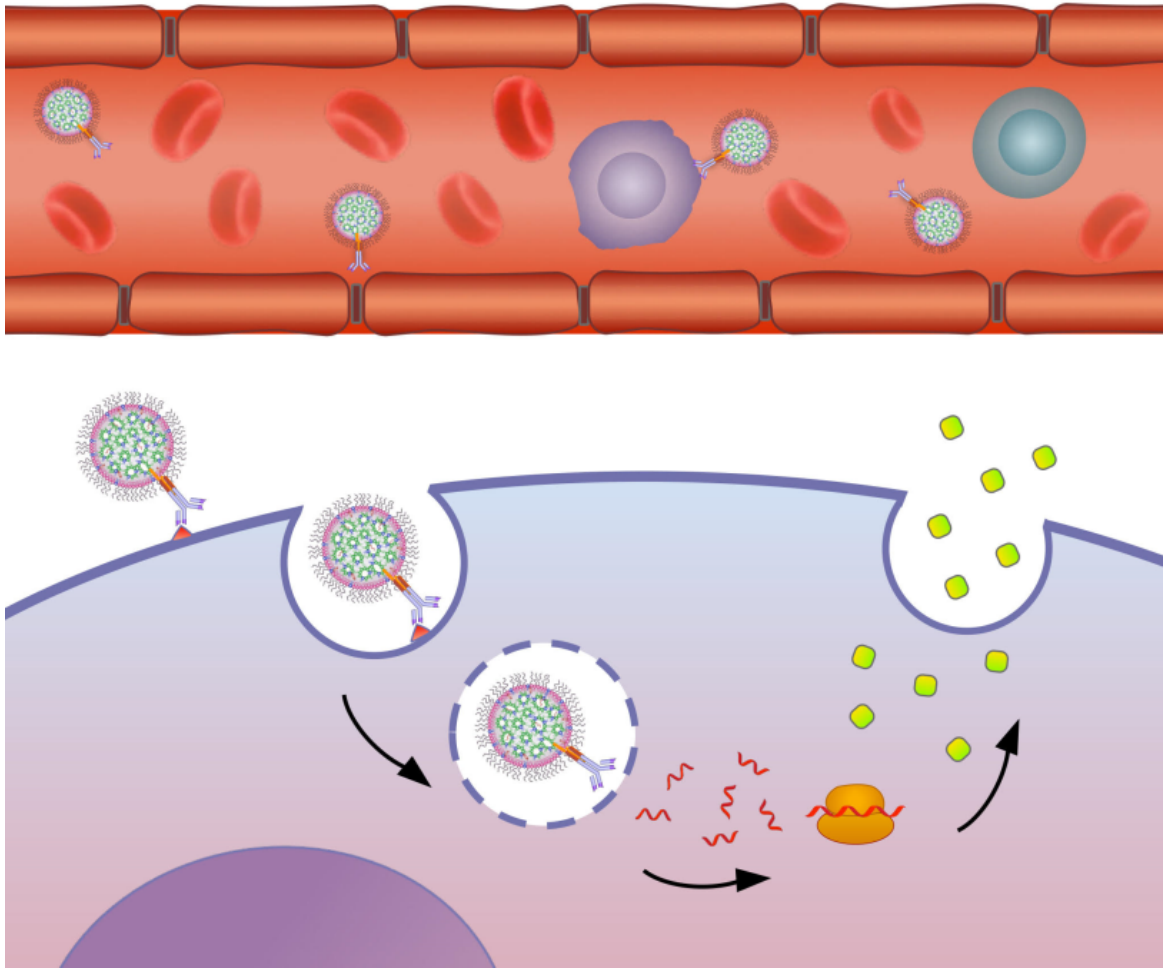






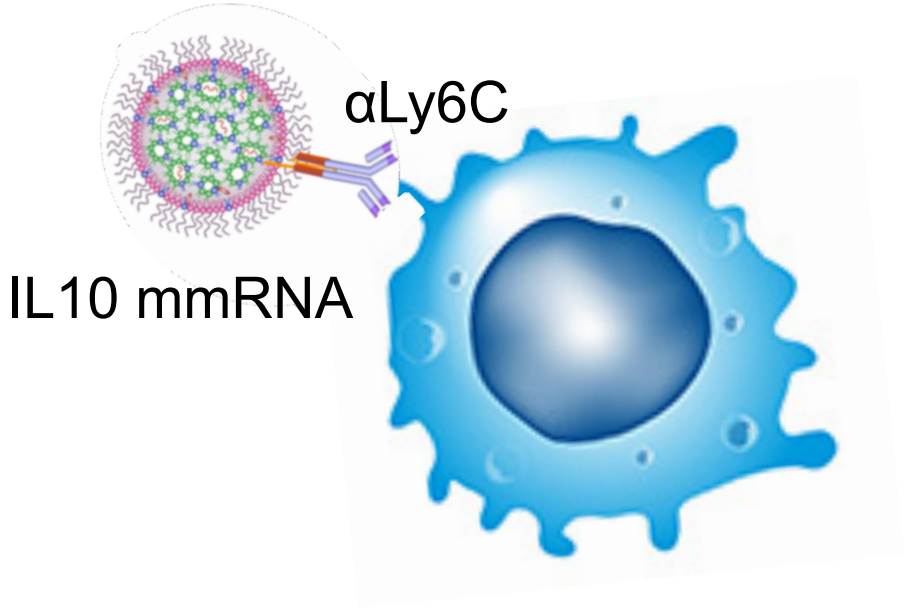
Veiga N. et al. Nature Communications 2018

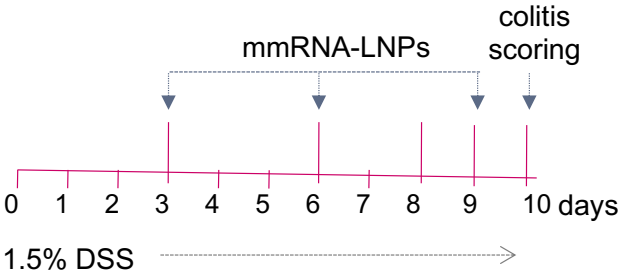
Therapeutic effect using targeted in-vivo IL10 expression

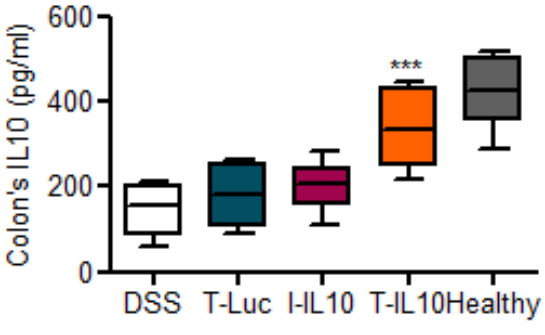


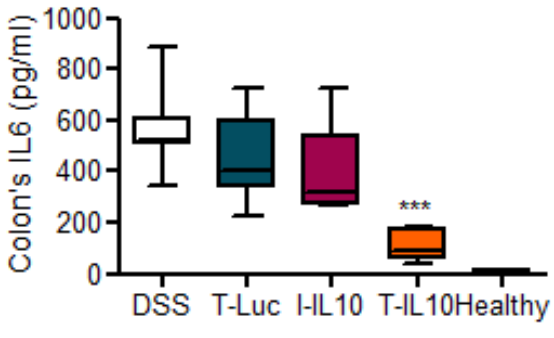
Veiga N. et al. Nature Communications 2018

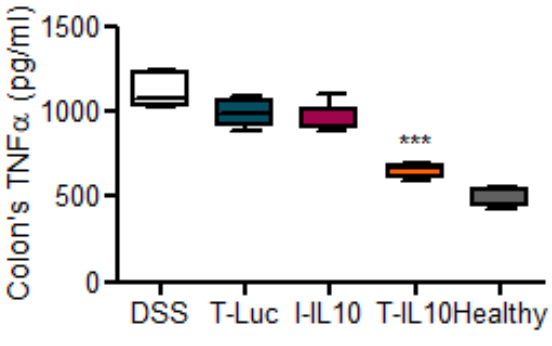
Immunomodulation *in-vivo*





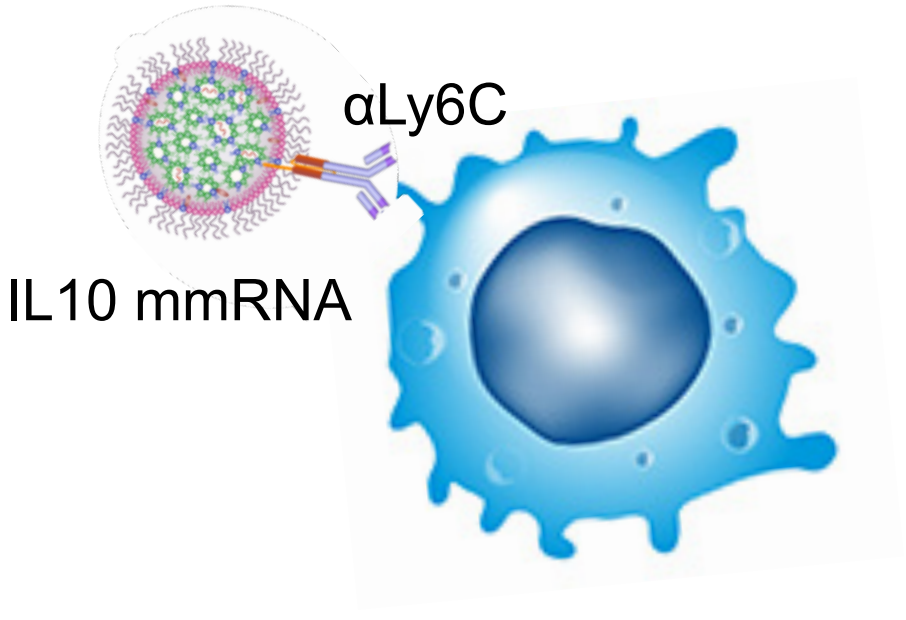


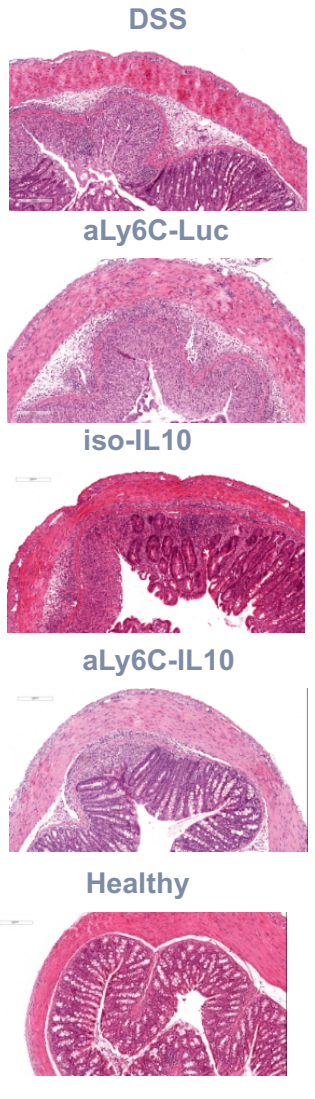


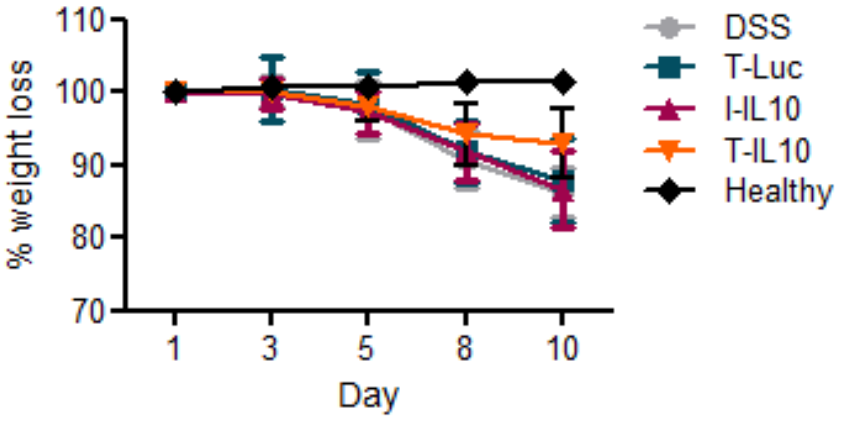


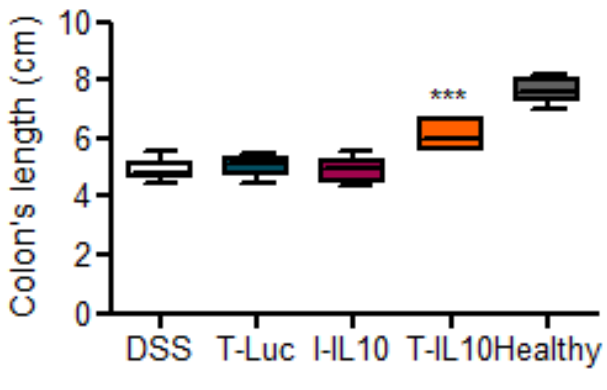
Veiga N. et al. Nature Communications 2018

Immunomodulation *in-vivo*







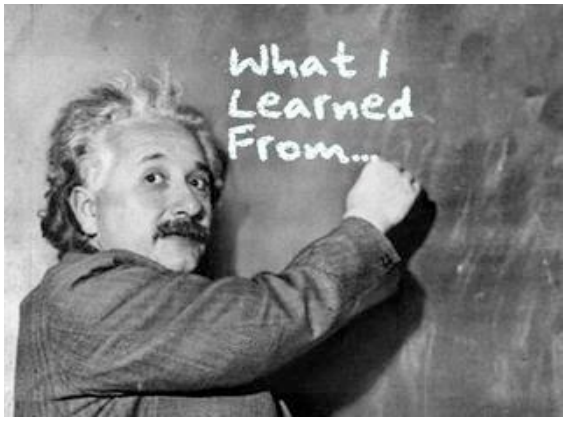


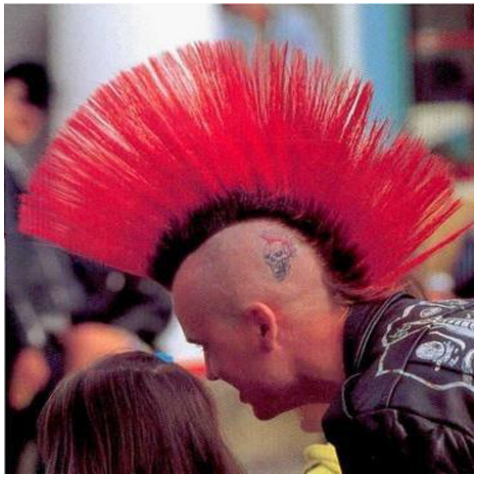
Veiga N. et al. Nature Communications 2018

Vision

Endless opportunities for a precise gene manipulation

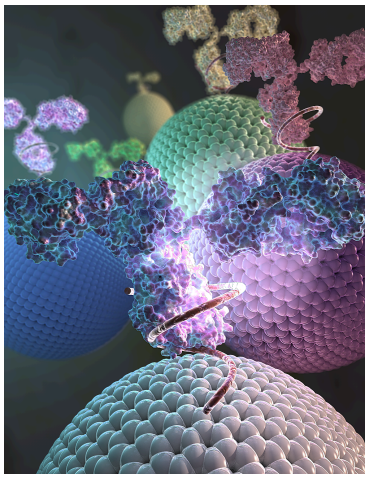
Where are we going in carrier-mediated RNA therapy ?





Avoiding MNP

High specificity and functionality



Fast internalization and burst release (e.g. NA)

Better RNA drugs (siRNAs, mmRNA) and Improve genome editing)

D
alit
Landesman-Milo,
Ph.D

Inbal
Hazan-Halevy
,Ph.D

Meir
Goldsmith, Ph.D

Leona Kampel

Gal Finkelstein

Srinivas
Ramishetti,
Ph.D

Niles Dammes

Oren Pinshow

Stephanie Rietwyk,
Ph.D.

Olga Karpov
Ph.D

Keren Cohen

Shoshy Mizrahy

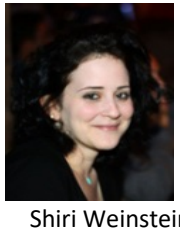
Peer Lab
Precision Nanomedicine

Eli Muchtar, MD

Assaf Persitz, MD

Hagit Bar-Sheet

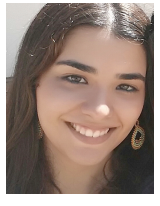
Ranit Kedmi, Ph.D.



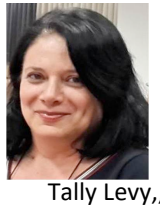
Shiri Weinstein

Neta Soffer-Tsur

המרכז לחקר המטאונקולוגי
על שם ורדה ובעז דותן



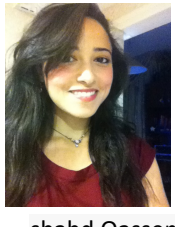
Yasmine Granot



Tally Levy,, MD

Brandon Ng

Daniel
Rosenblum

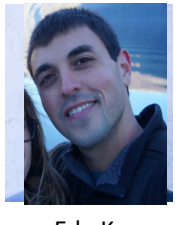


shahd Qassem

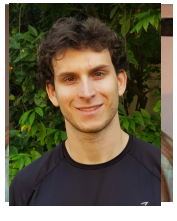
Nuphar Veiga

Wolf
Raichenbach

Manu Singh, Ph.D.



Edo Kon



Gilad Mechtinger

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