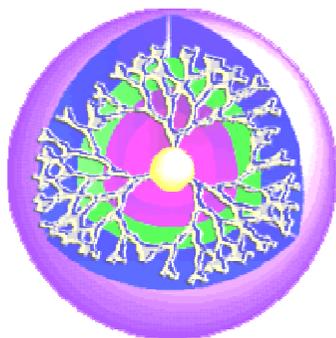




# Dendrimers as nanovectors for drug delivery



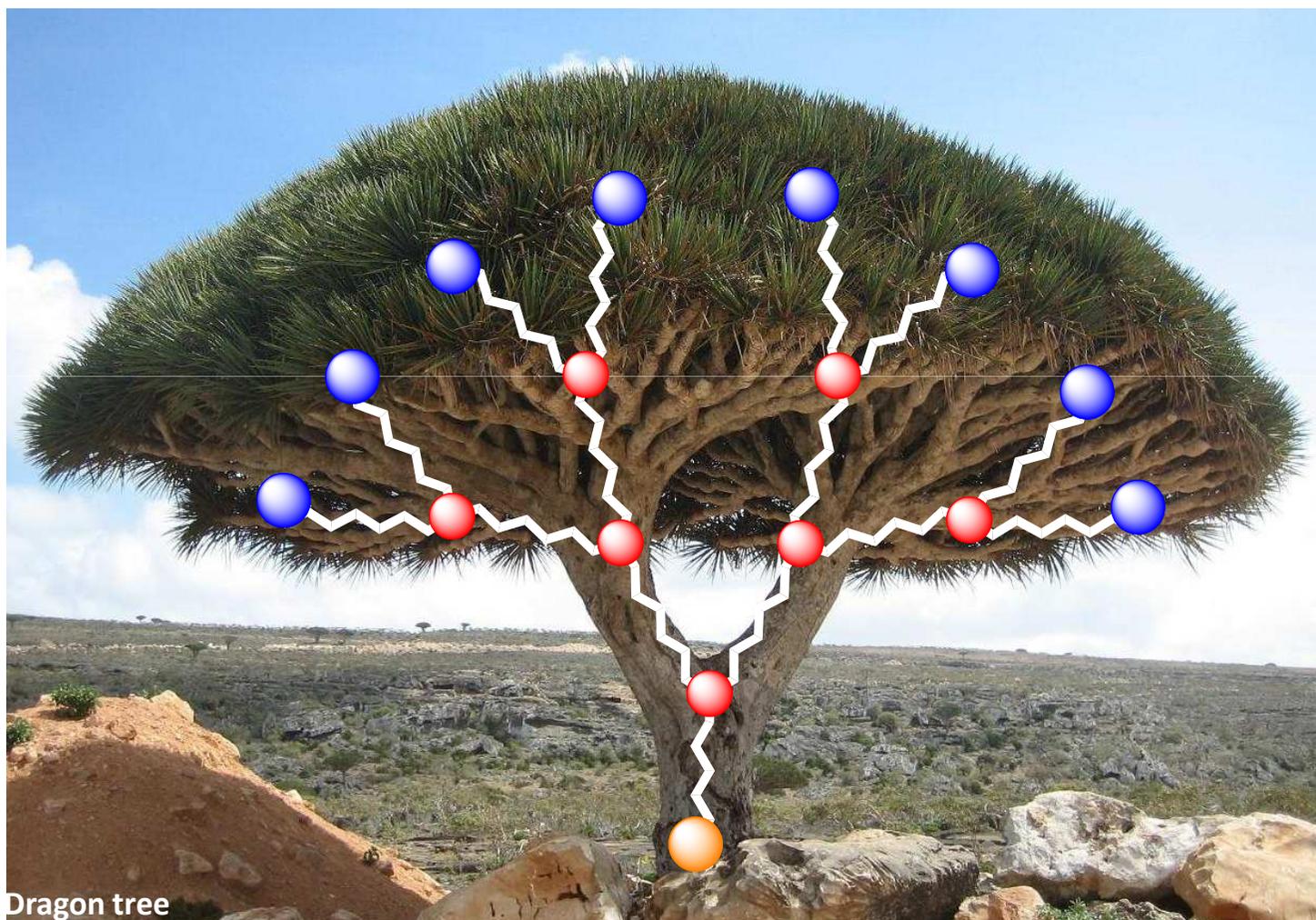
**Dr. Ling PENG**

Centre Interdisciplinaire de Nanoscience de Marseille  
CNRS UMR 7325, Marseille, France

Workshop NANO, 28/03/2014



Dendrimer : dendron (tree) + meros (part)



**Dendrimers: synthetic macromolecules with dendritic structures**

# Dendritic structures created by nature

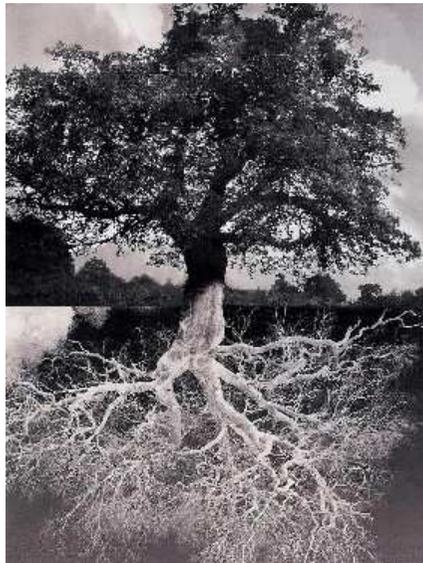
Examples:

tree,  
root,  
...

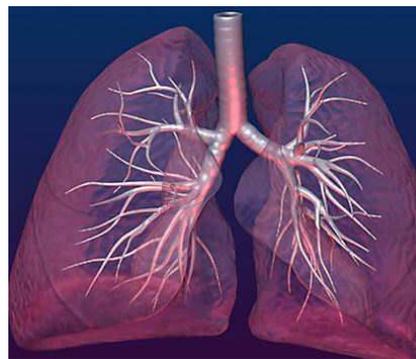
lung,  
kidney,  
...

neurons,  
...

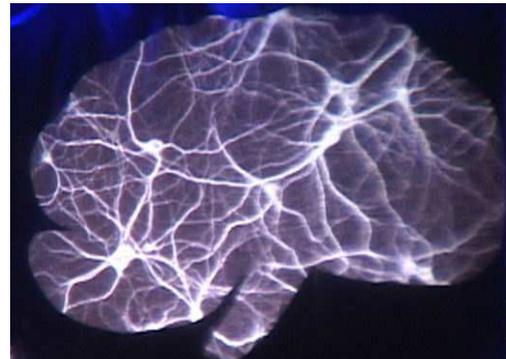
glycogen,  
amylopectin,  
...



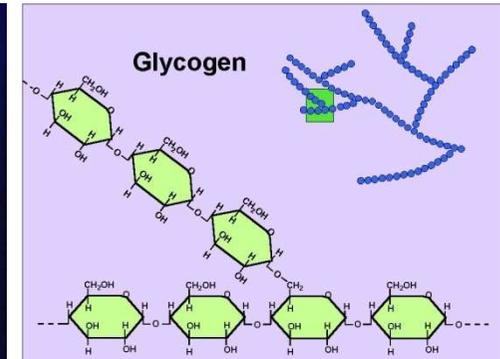
m



cm



$\mu\text{m}$



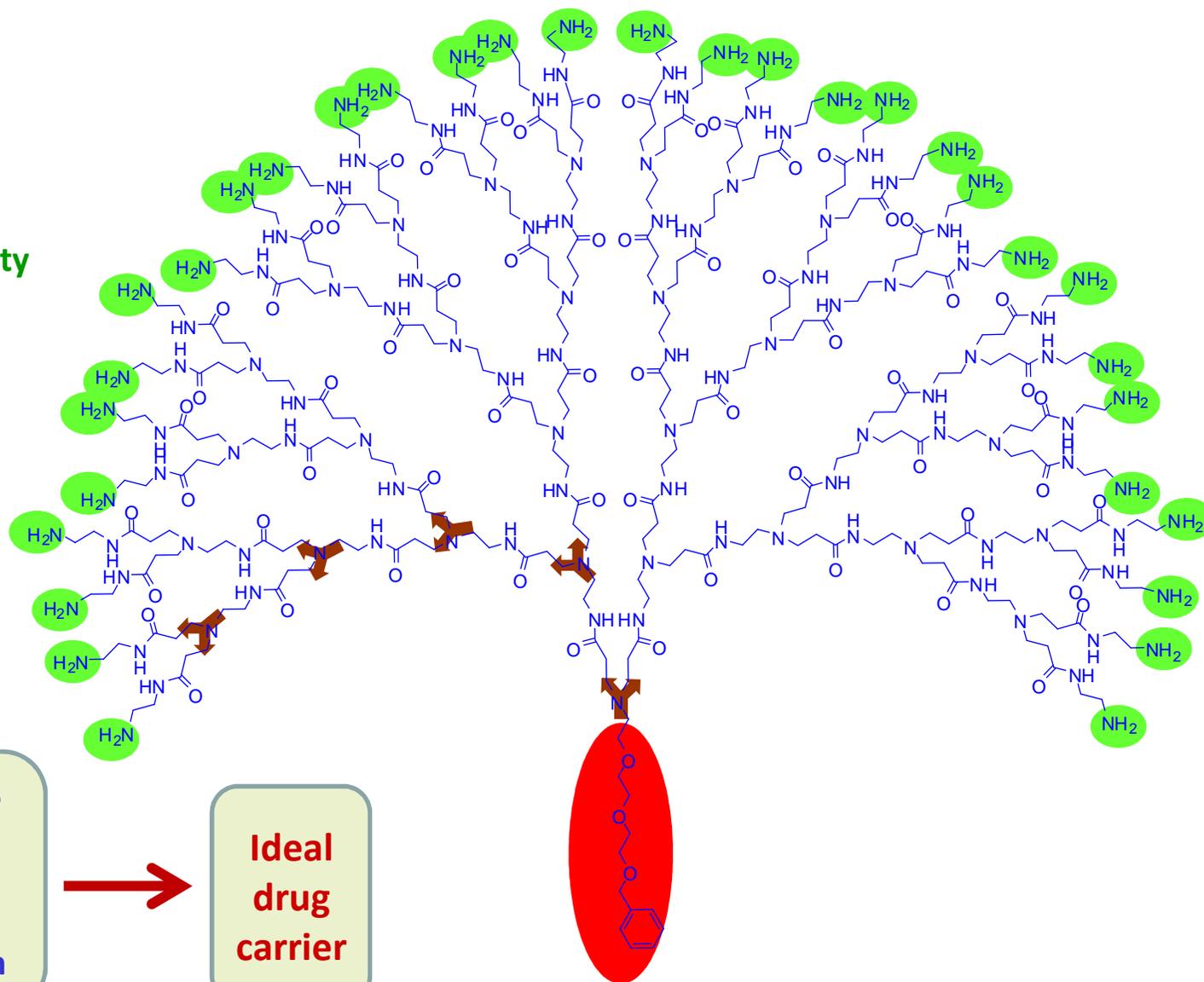
nm

# A dendrimer made by chemists

Core

Branching unit

Surface functionality

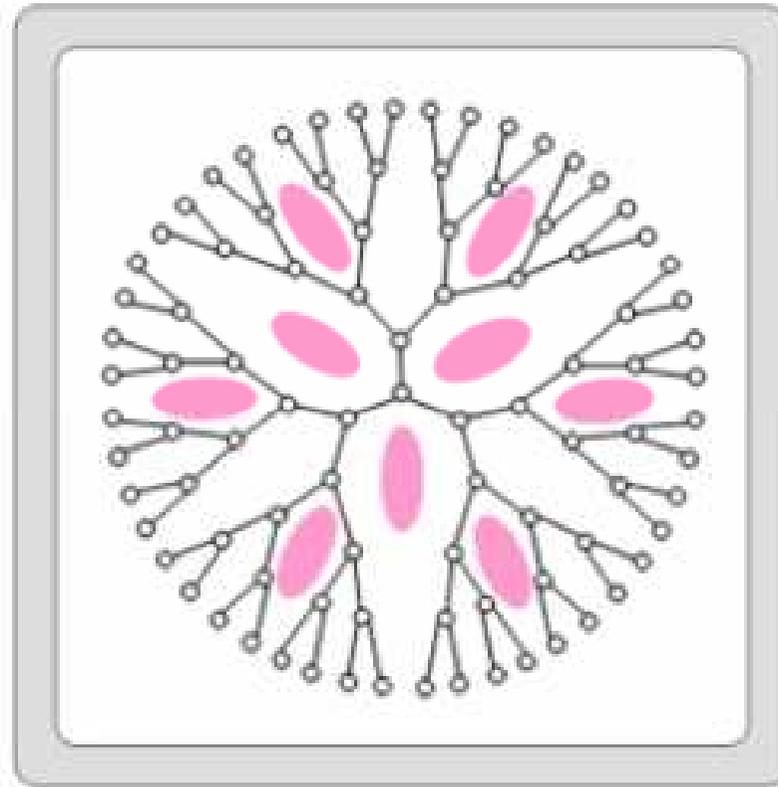


well-defined structure  
unique multivalency  
various cavities  
facile functionalization



Ideal  
drug  
carrier

## Anticancer cisplatin/PAMAM complexes



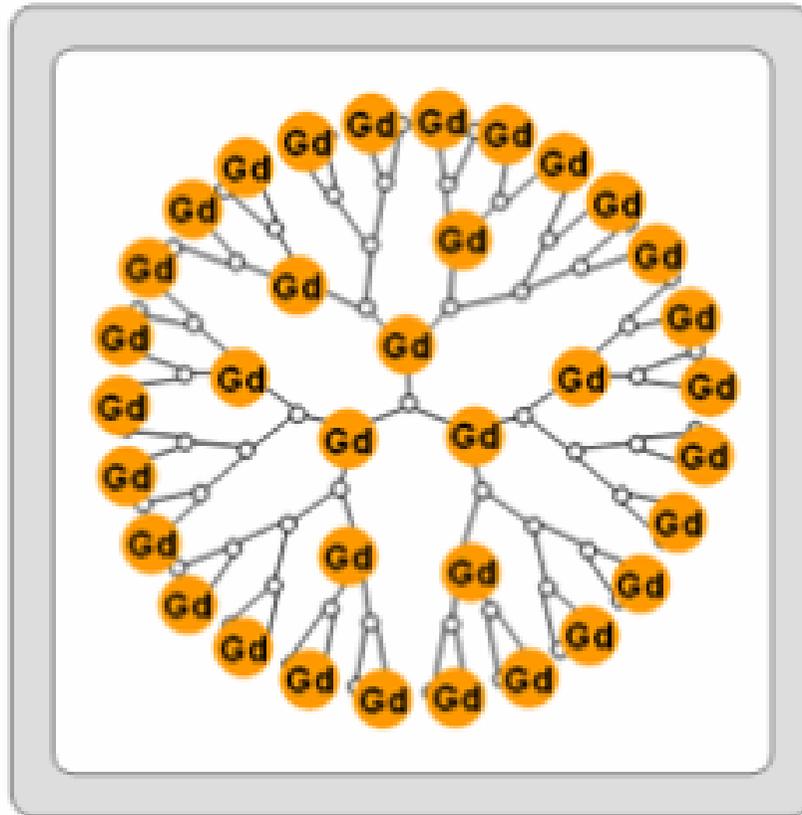
- increase drug solubility by 10-fold
- increased drug uptake in tumor cell by 5-fold
- decreased toxicity by 3-fold

in development

## 2. Biological applications

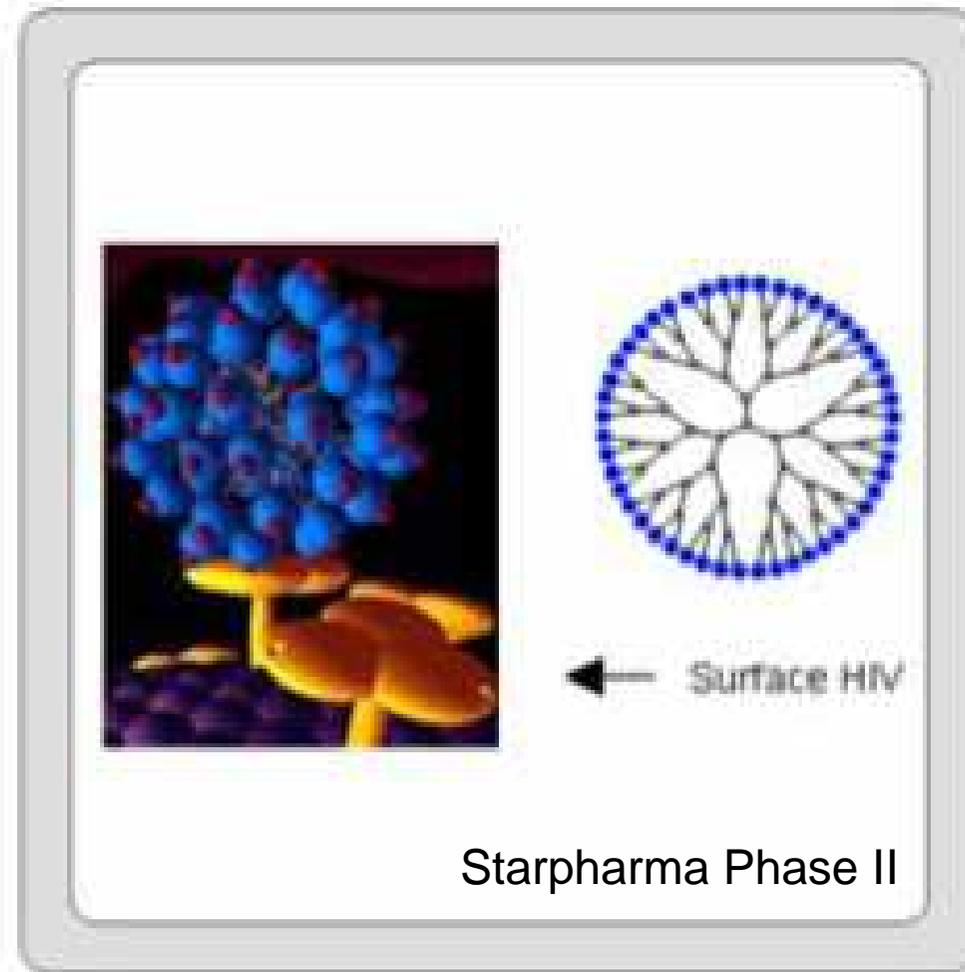
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### Magnetic Resonance Imaging (MRI) reagent



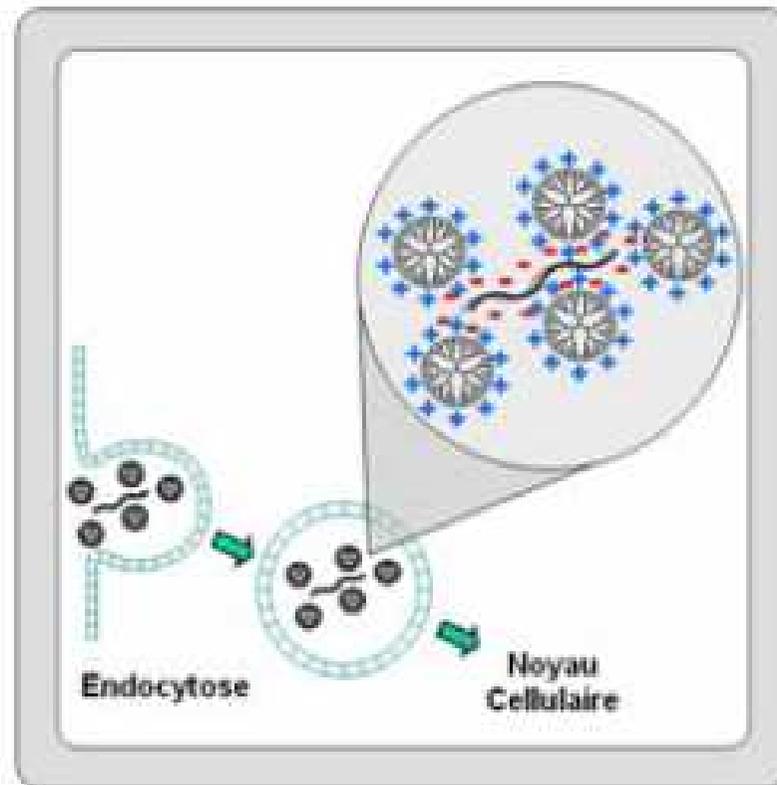
by Schering and Dendritech

## Dendrimer anti-HIV drug: Vivagel



Negatively charged poly(lysine)sulfate bind to the positively charged HIV surface

## Delivery system for DNA molecules

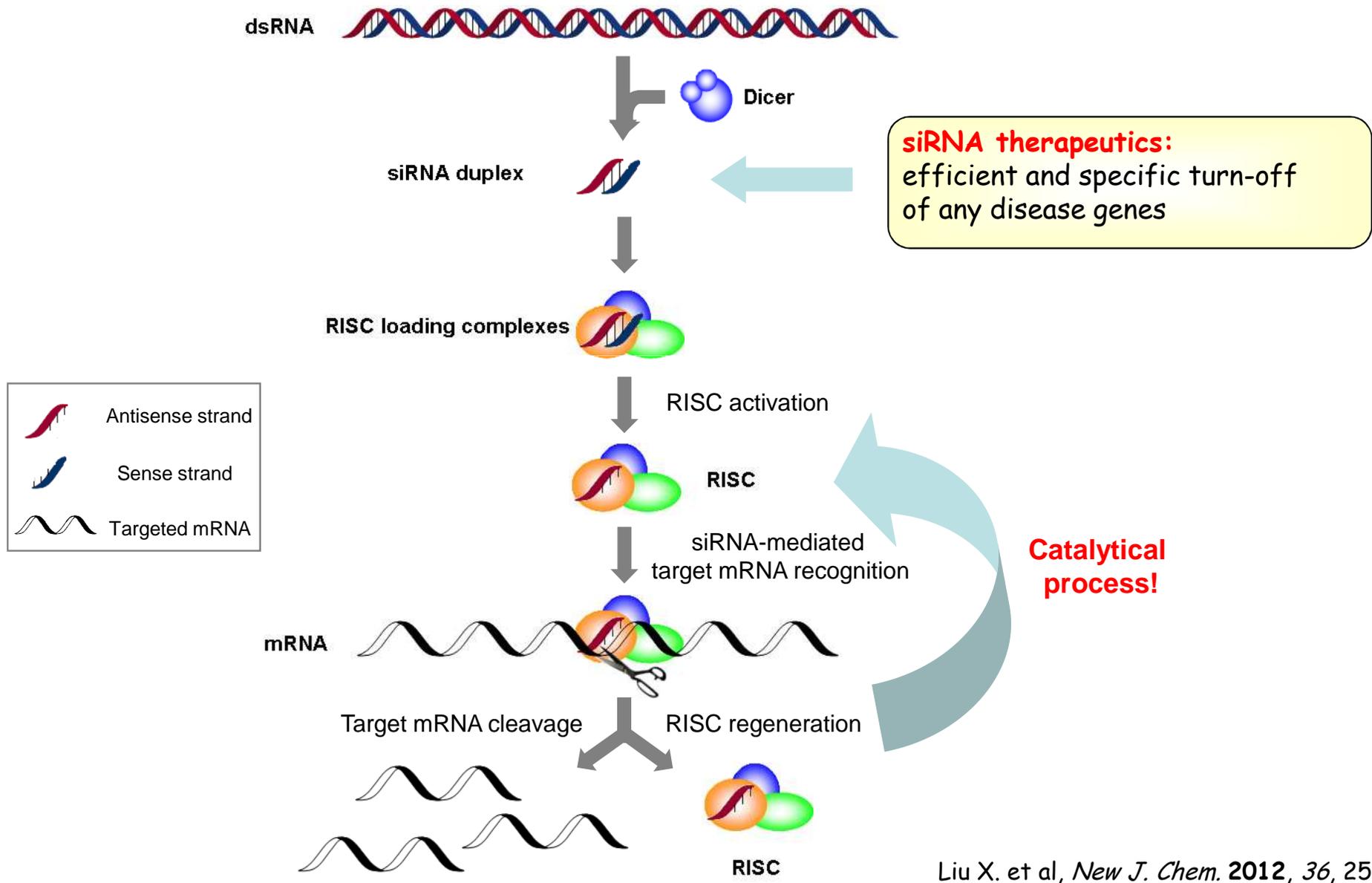


**SUPERFECT<sup>®</sup>**

commercialized by QIAGEN, Sigma-Aldrich

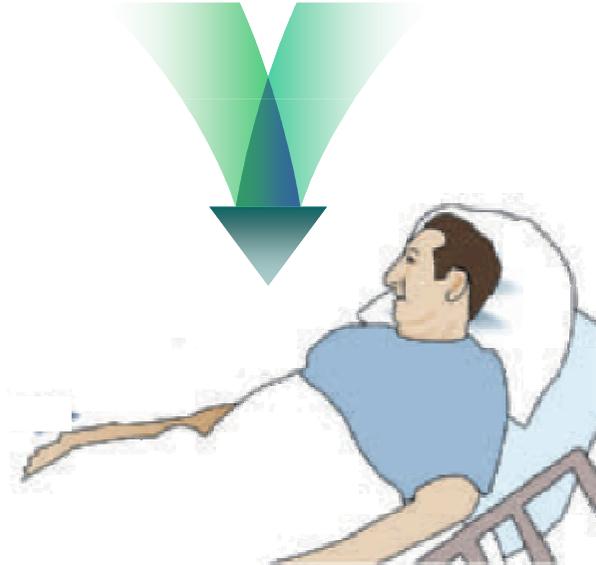
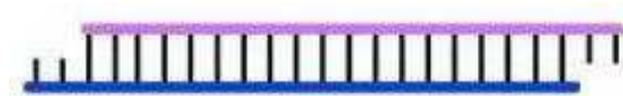
# Functional delivery of RNAi therapeutics

# Gene therapy: siRNA-based RNA interference



## Gene therapy: siRNA-based RNA interference

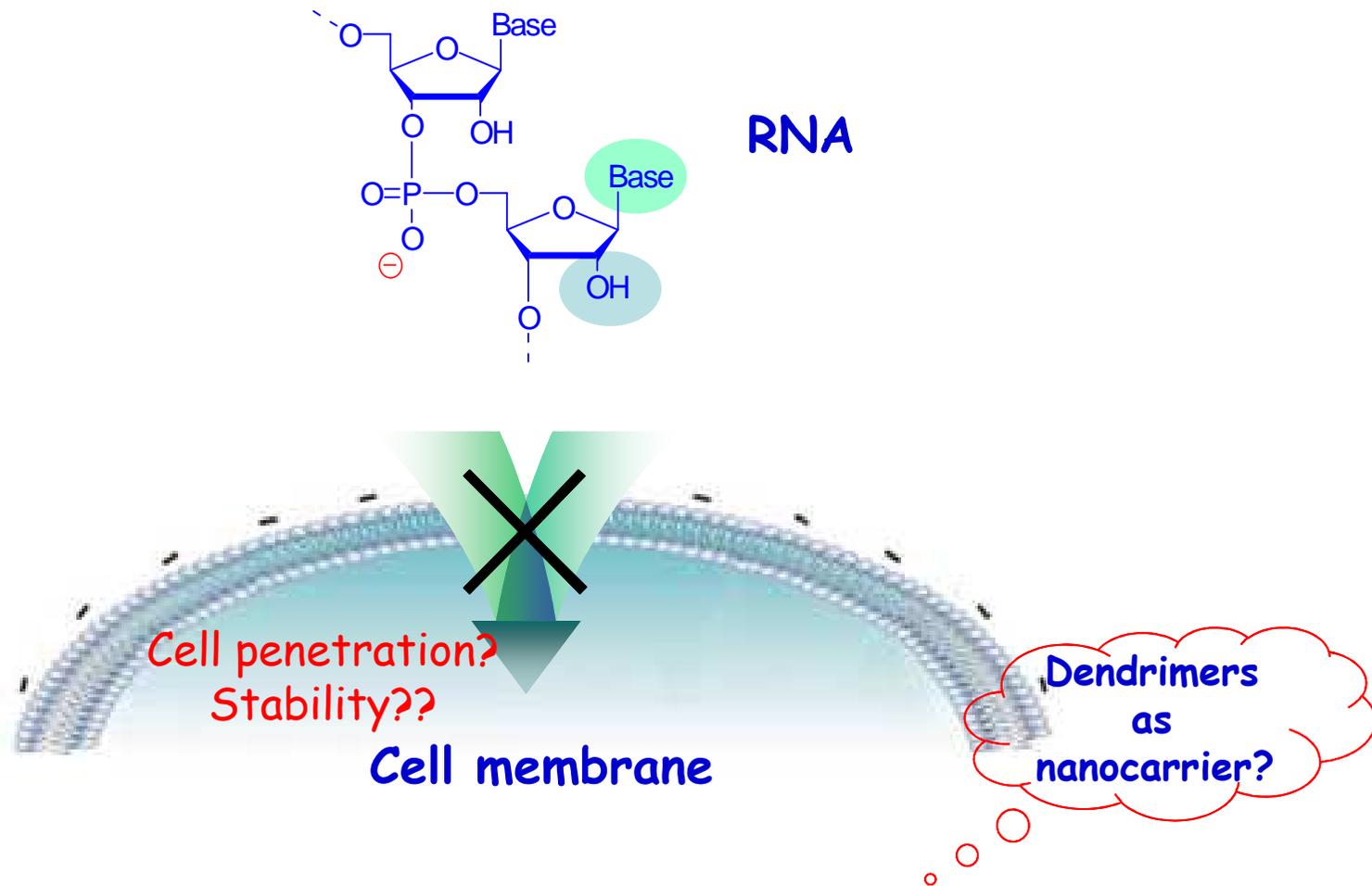
### siRNA therapeutics



**“Turn off”  
any disease gene**

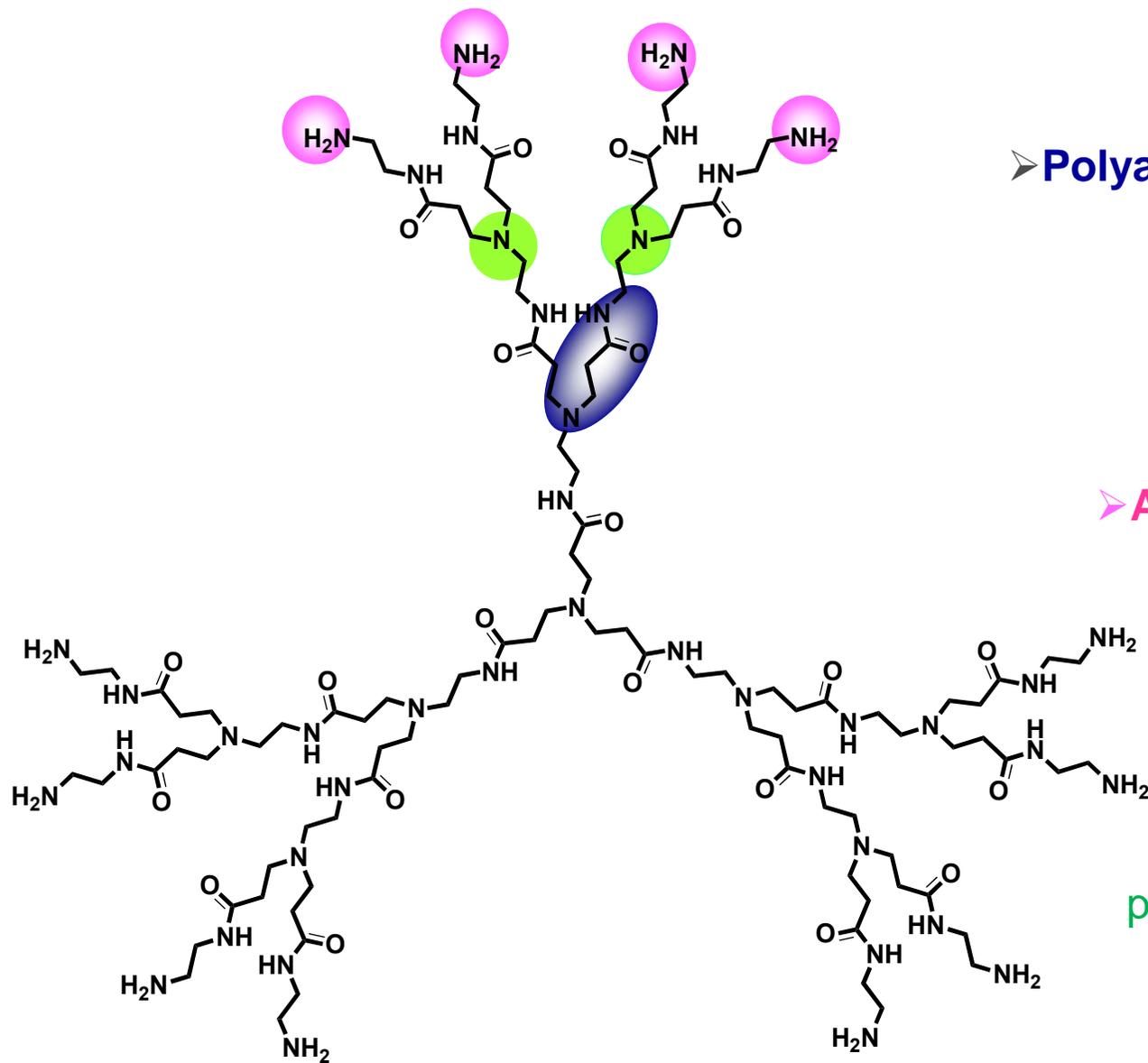
- 😊 Specific and efficient silencing of disease genes
- 😊 General treatment for any diseases, even for undruggable gene

## RNAi therapeutics



How RNA therapeutics can enter into the cells efficiently and safely?

# Polyamidoamine (PAMAM) Dendrimers



➤ **Polyamidoamine branching units**

Protein mimicking  
Biocompatibility

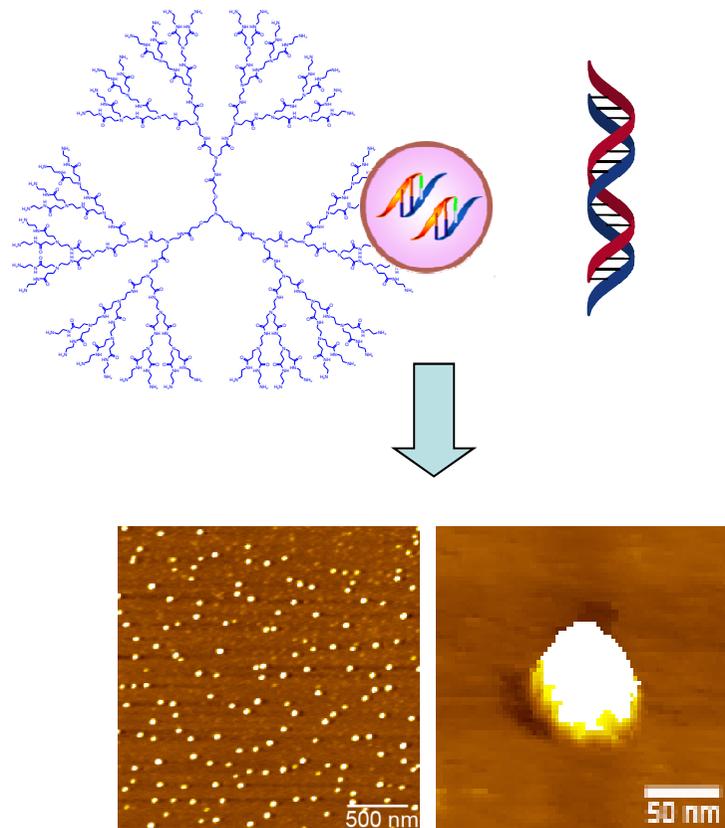
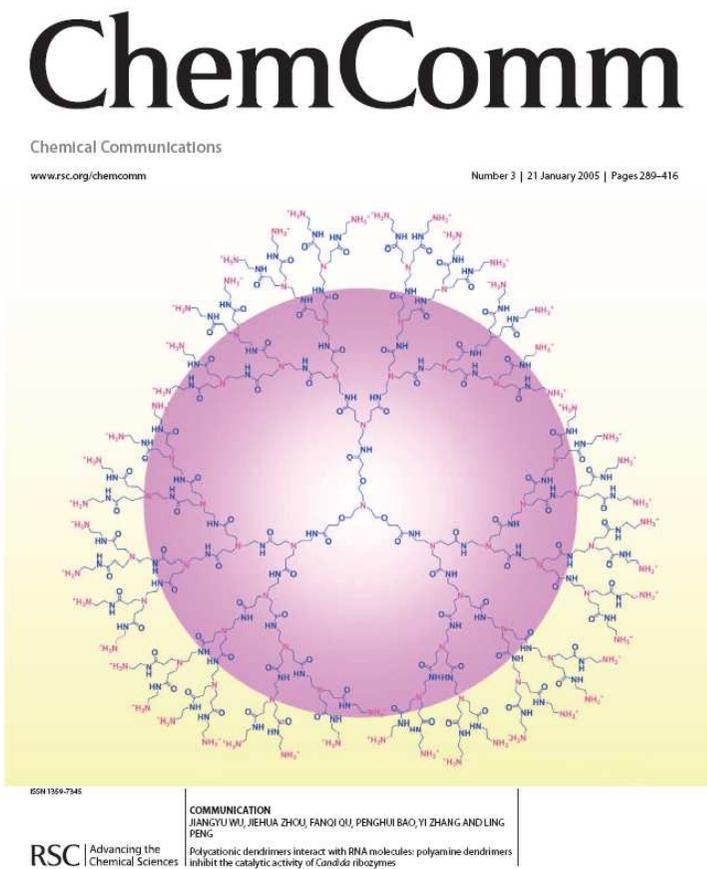
➤ **Amine terminal groups**

Binding to nucleic acid

➤ **Tertiary amine interior**

Acting as “Proton sponge”  
promote the endosome escape

## First report on RNA/dendrimer interaction



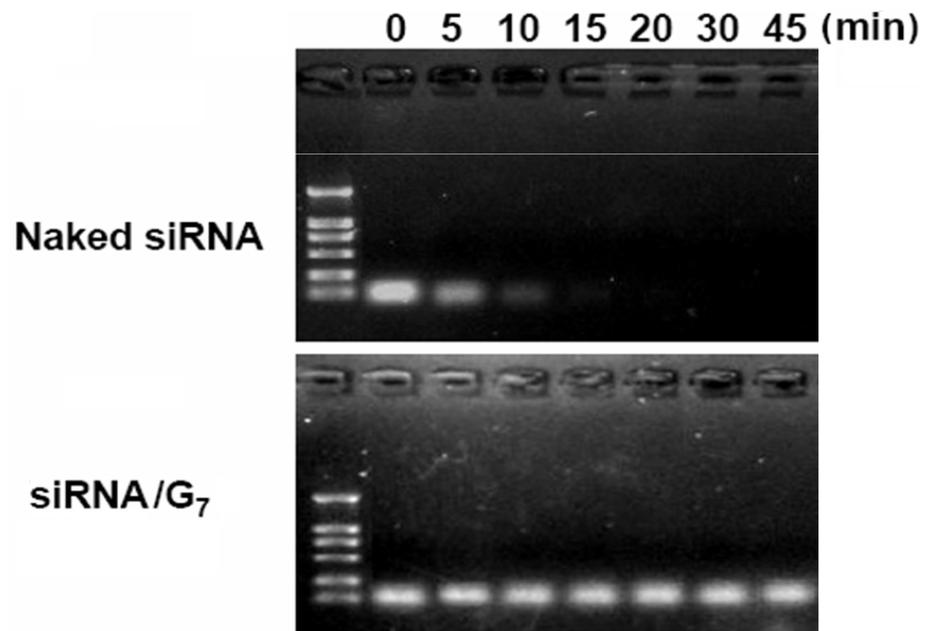
Nanoscale complex

Wu J. et al, *Chem. Commun.* 2005, 313

Shen X. C. et al, *Org. Biomol. Chem.* 2007, 5, 3674

## Dendrimers protect siRNA and promote cell uptake

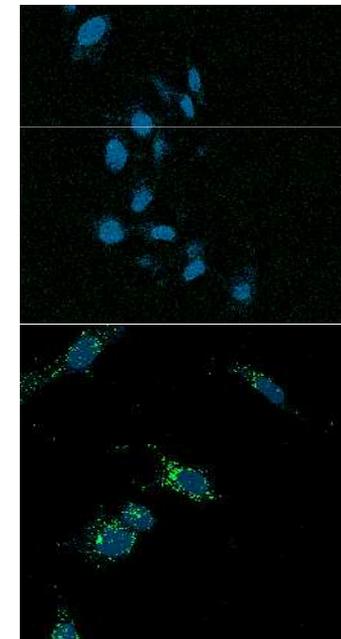
Protection from RNase



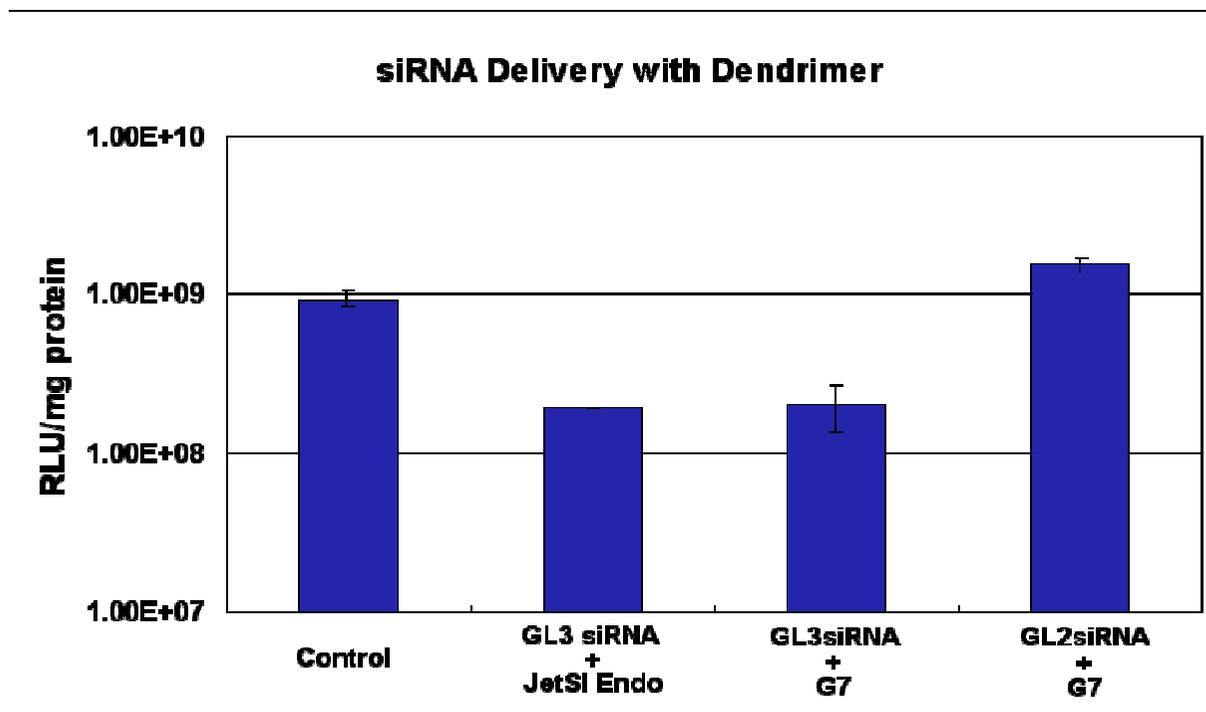
Promotion of cell uptake

Naked siRNA

siRNA/G<sub>7</sub>

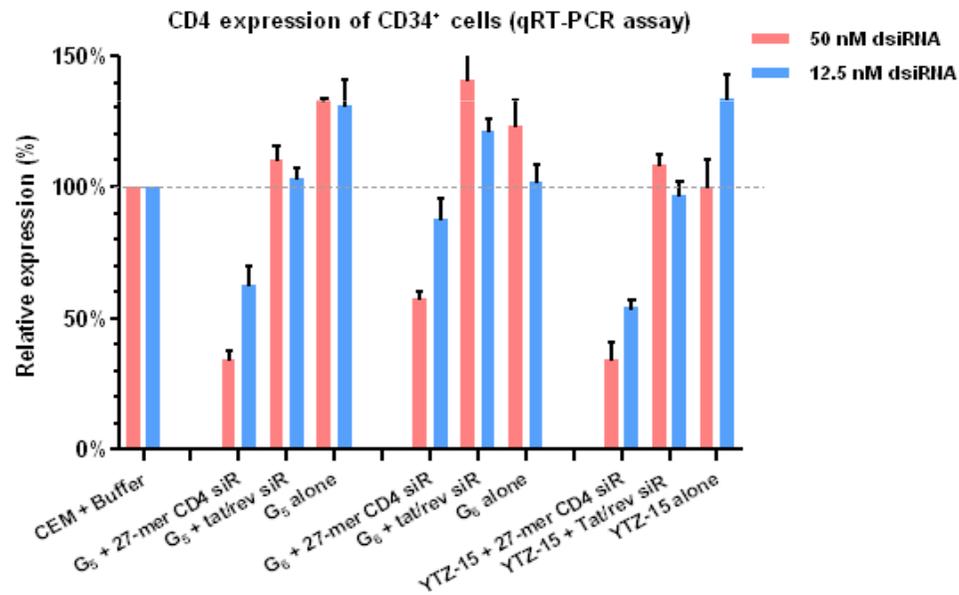


## Effective and specific gene silencing



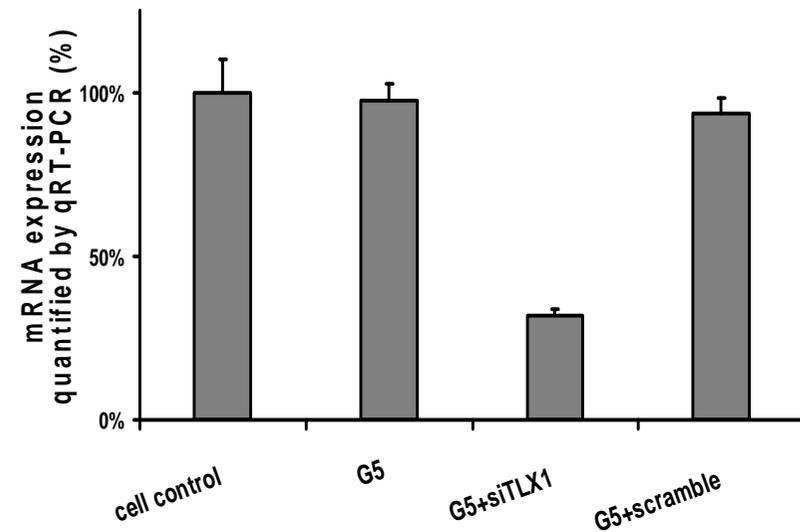
## Gene silencing in stem cells

### CD4 expression (CD34+)



Zhou et al, *unpublished*

### TLX expression (Gliomas)



Lang et al *PLoS ONE*, 2012, 7, e36248

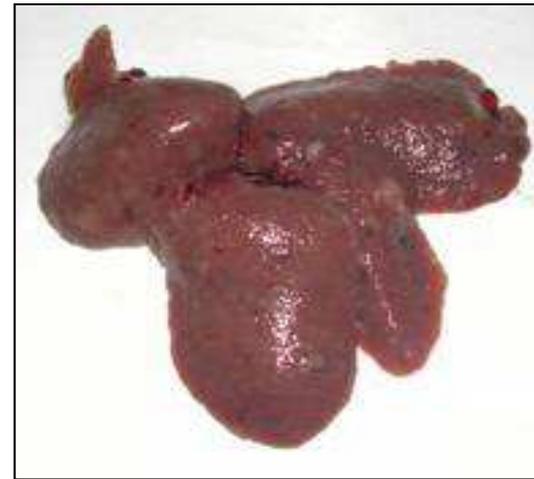
## Functional RNA delivery for anticancer treatment

**Control**



Liver of male Wistar rat

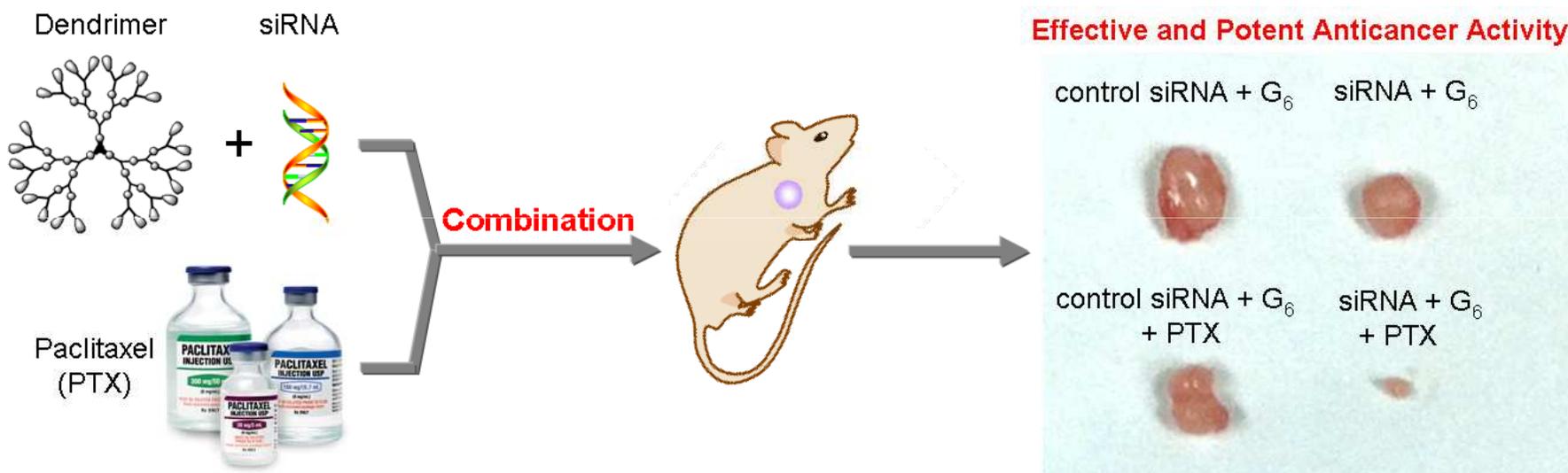
**Dendrimer/RNA**



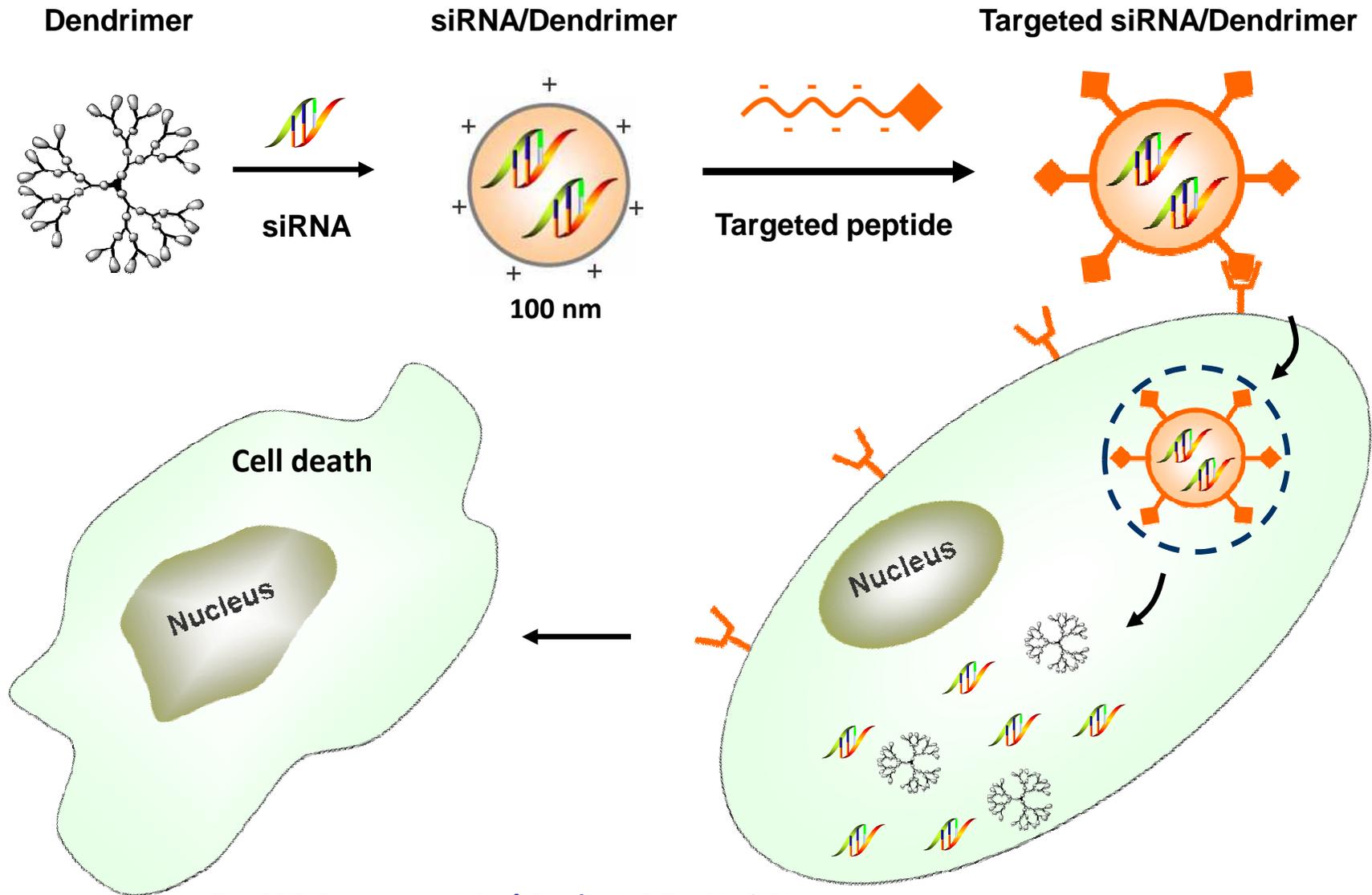
Liver of male Wistar rat

**Significant tumor reduction!**

# Combination of siRNA and paclitaxel to treat ovarian cancer

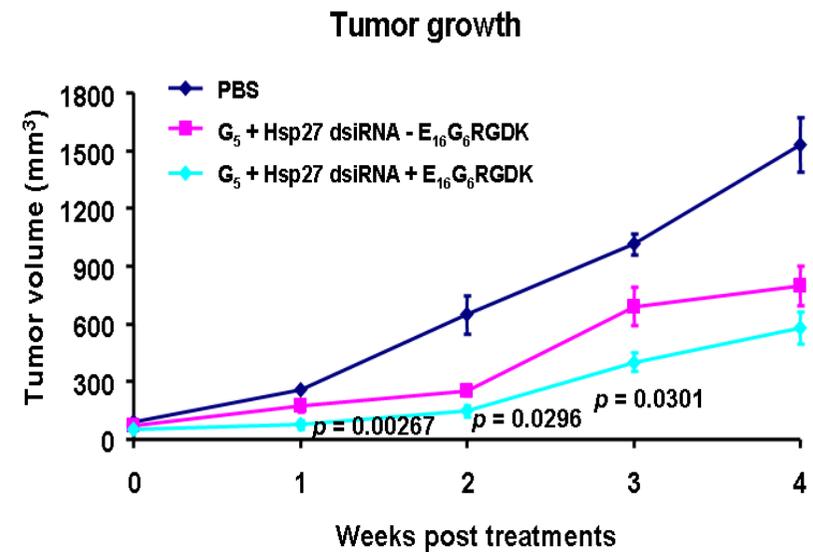
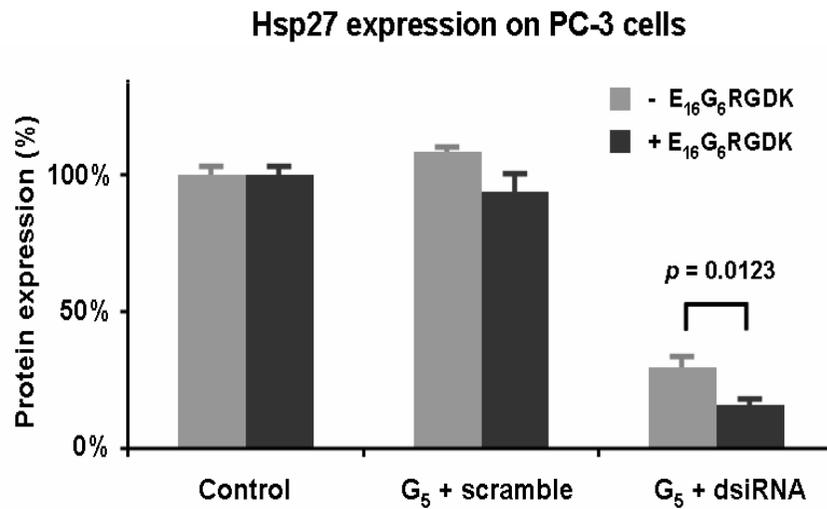


# Targeted delivery of RNAi drugs in cancer therapy

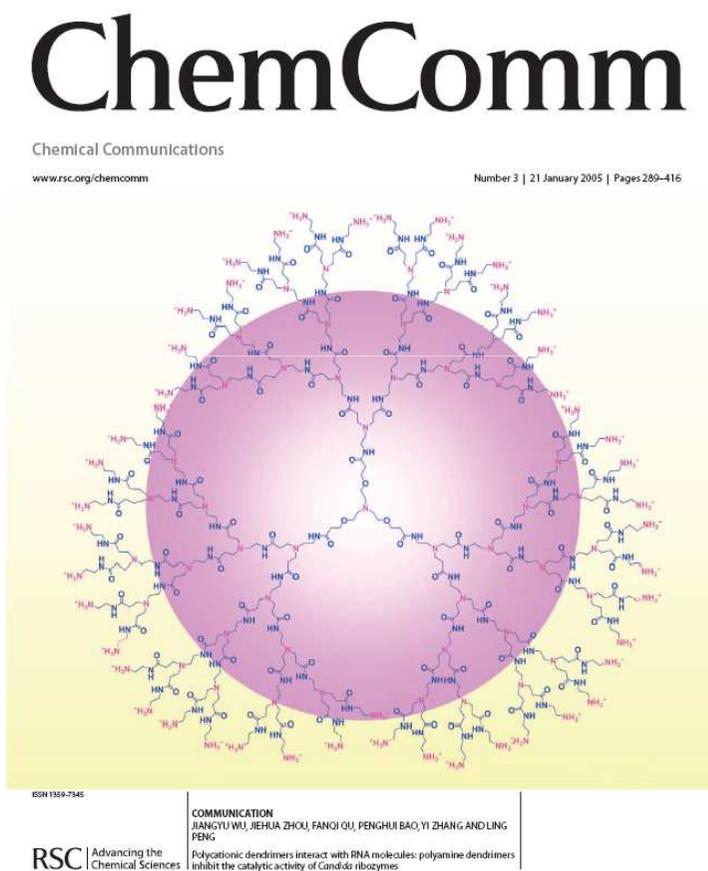


# Dendrimers as nanovectors for targeted siRNA delivery

## Targeted delivery of RNA therapeutics to treat prostate cancer



## PAMAM dendrimers for nucleic acid delivery



molecular  
pharmaceutics  
march 2012  
volume 9 number 3  
pubs.acs.org/molecularpharmaceutics

Featured topic:  
biological applications  
of dendrimers

ACS Publications  
MOST TRUSTED. MOST CITED. MOST READ.  
www.acs.org

Scheduled for clinic trials in USA, UK and China  
**Delayed due to the GMP production of dendrimer**

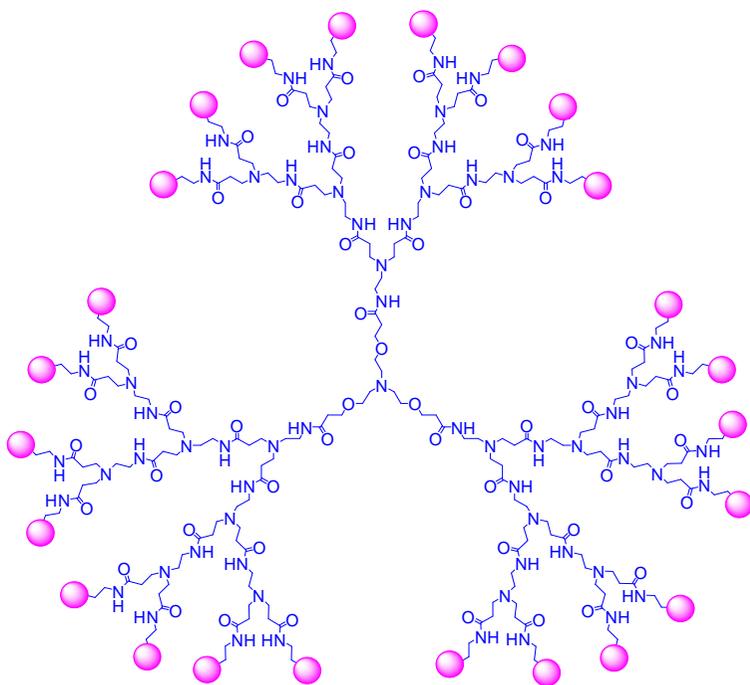
# **Challenges**

**smaller dendrimer**

**easier synthesis**

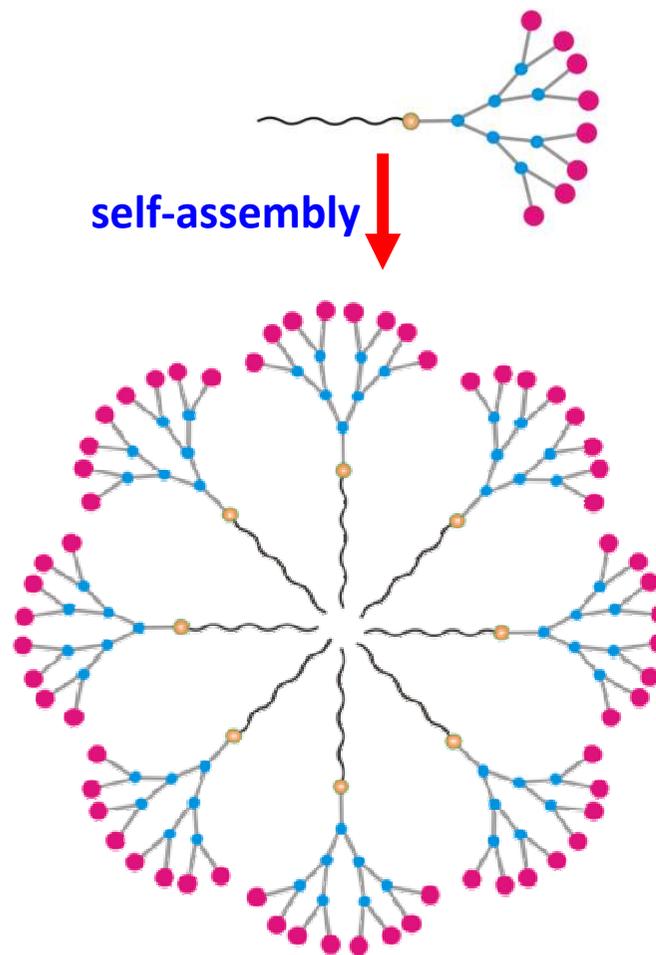
## Self-assembly to supramolecular dendrimer

Structure flexible dendrimer



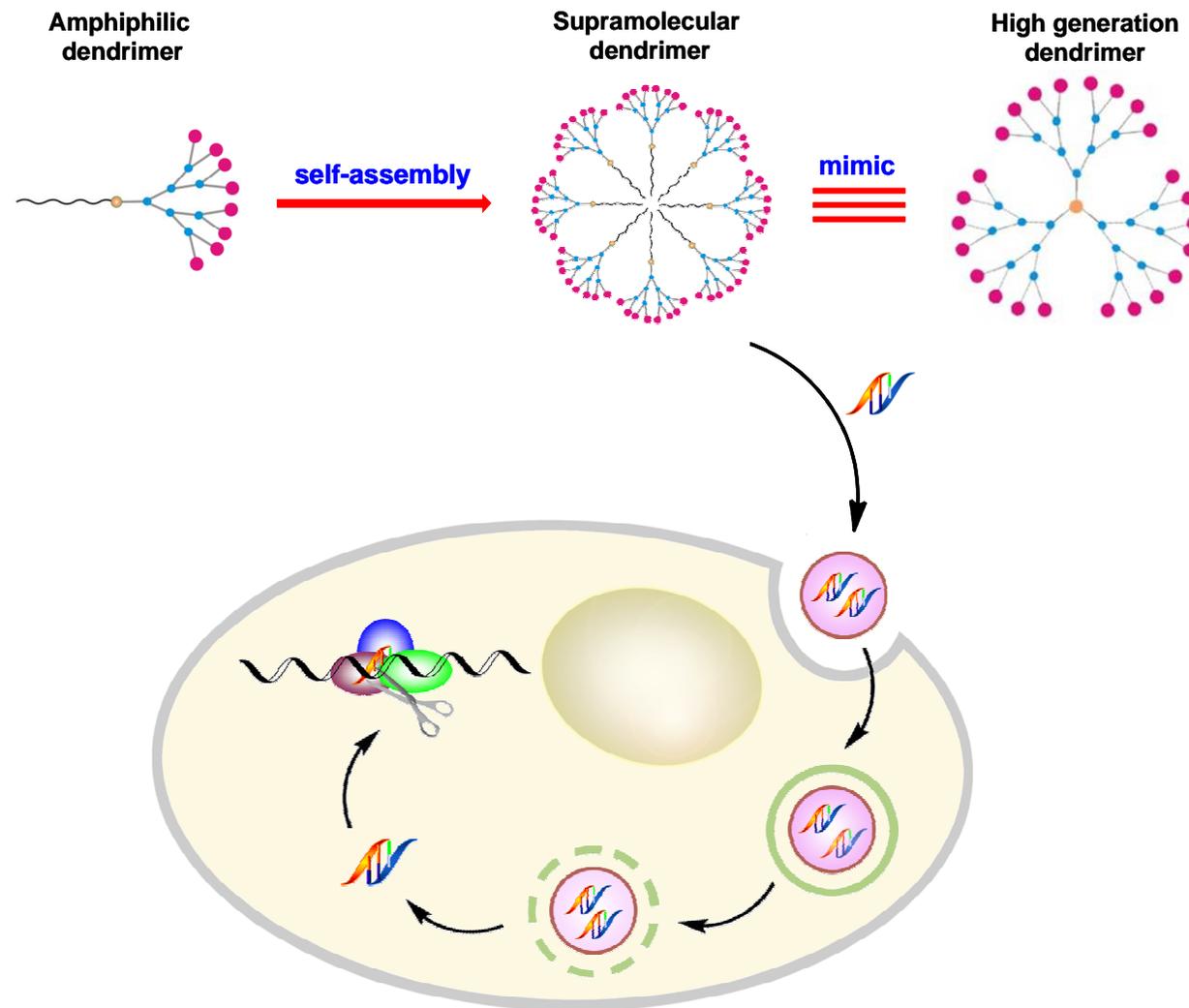
Zhou J. et al, *Chem. Commun.* **2006**, 2362.

self-assembly

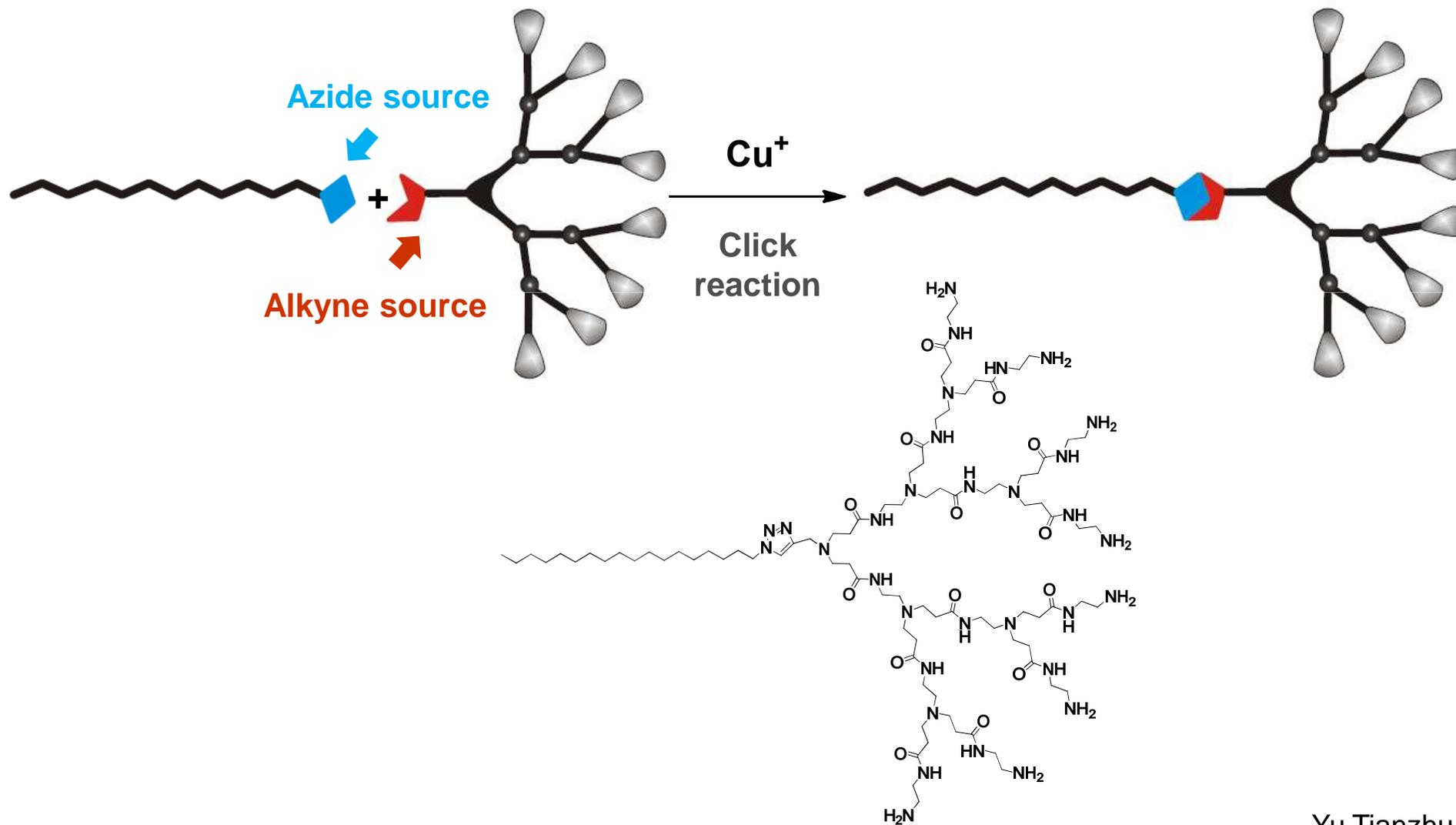


Supramolecular dendrimer

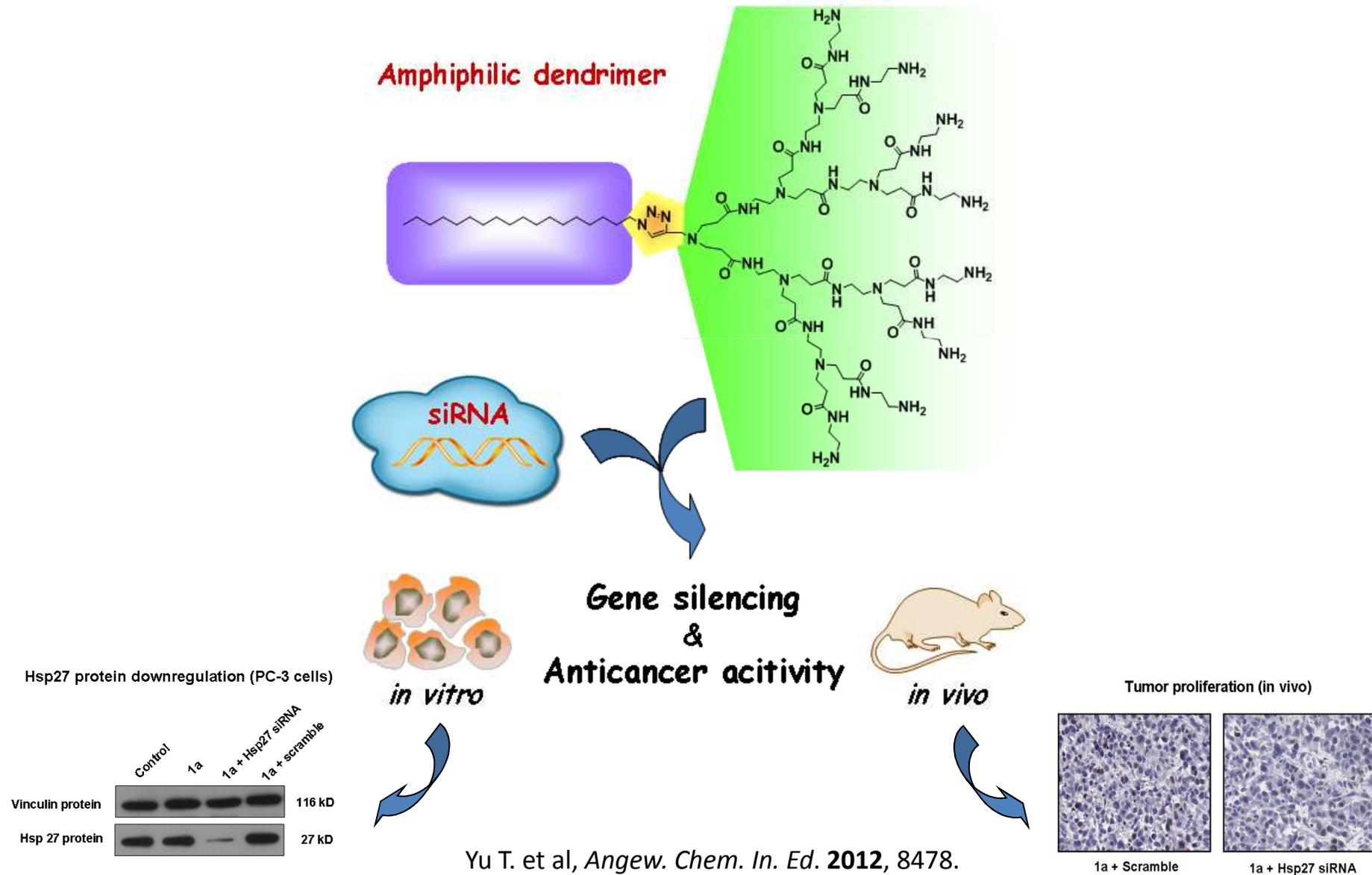
## Self-assembly to supramolecular dendrimer



## Dendrimer synthesis



## Effective vector for siRNA delivery in vitro and in vivo



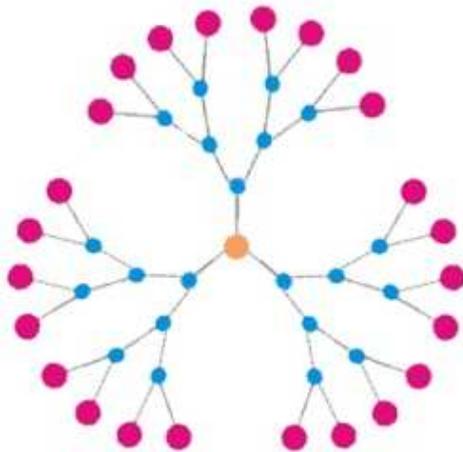
## Amphiphilic dendrimer

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### Self-assembly of amphiphilic dendrimer to supramolecules

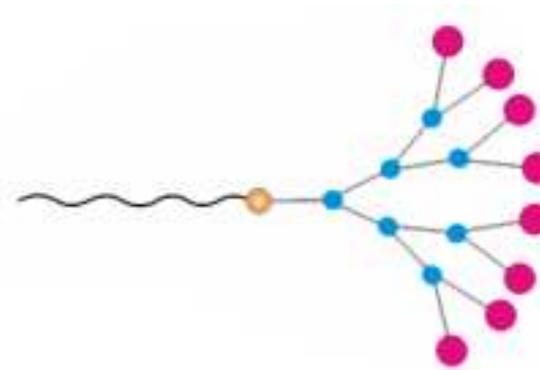
**High generation dendrimer**

**Molecular weight  
21960**



**Amphiphilic dendrimer**

**Molecular weight  
1949**



# Conclusions

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## Promise

Dendrimers are promising nanovectors for siRNA and drug delivery  
(in various disease models)

## Challenge

- Enhancing efficiency
- Reducing toxicity
- Targeted delivery

## Dendrimers as nanovectors for drug delivery

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### **Future plans in Horizon 2020:**

- 1. Strive for clinical trials**
- 2. Develop personalized medicine**
- 3. Develop novel dendrimer nanocarrier for theranostics**

# Acknowledgement

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Beijing University, China

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# Acknowledgement

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Thank You !