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# A Drug Delivery Banquet Peptides and Polymers

Stefano Menegatti - CBE, BTEC, BME

**UNC Eshelman School of Pharmacy**

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# Who I am

- Stefano (“Stef”)
- Born in Ferrara (Italy) in 1984
- Yes, I do cook and like wine, etc. etc.

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# My Education

- **Università di Bologna (M.Sc. 2009)**
- **NC State University (Ph.D. 2013)**
- **UC Santa Barbara (2013-2015)**


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# Where can you find me

- EB 1 - Room 1054
- Email: smenega@ncsu.edu
- Office phone: 5-6398
- Labs: 1028, 1030, 1032

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# Menu of the Day

*Appetizer*

- Synthetic platelets
- DAFODIL liposomes

*Main course*

- DNA-peptide-drug conjugates
- Skin permeation

*Dessert*

- Self-gelling subcutaneous formulation

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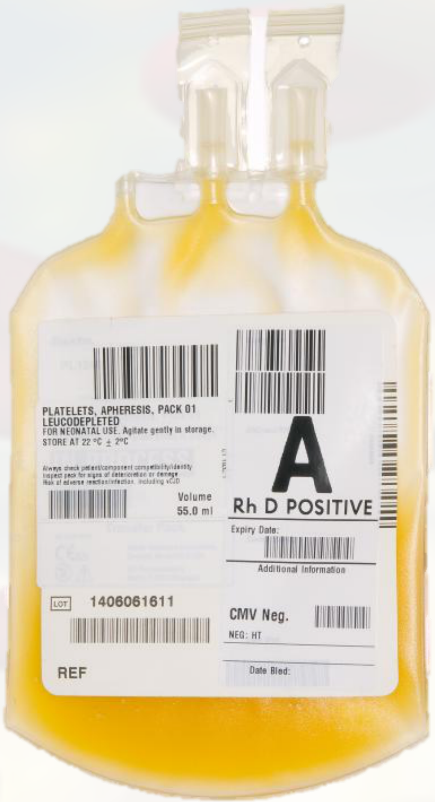
# Platelet-rich Plasma (PRP)

*Applications*

- Osteoarthritis
- Muscle tears
- Hemostasis

*Issues*

- Contaminants
- Short life
- Cost

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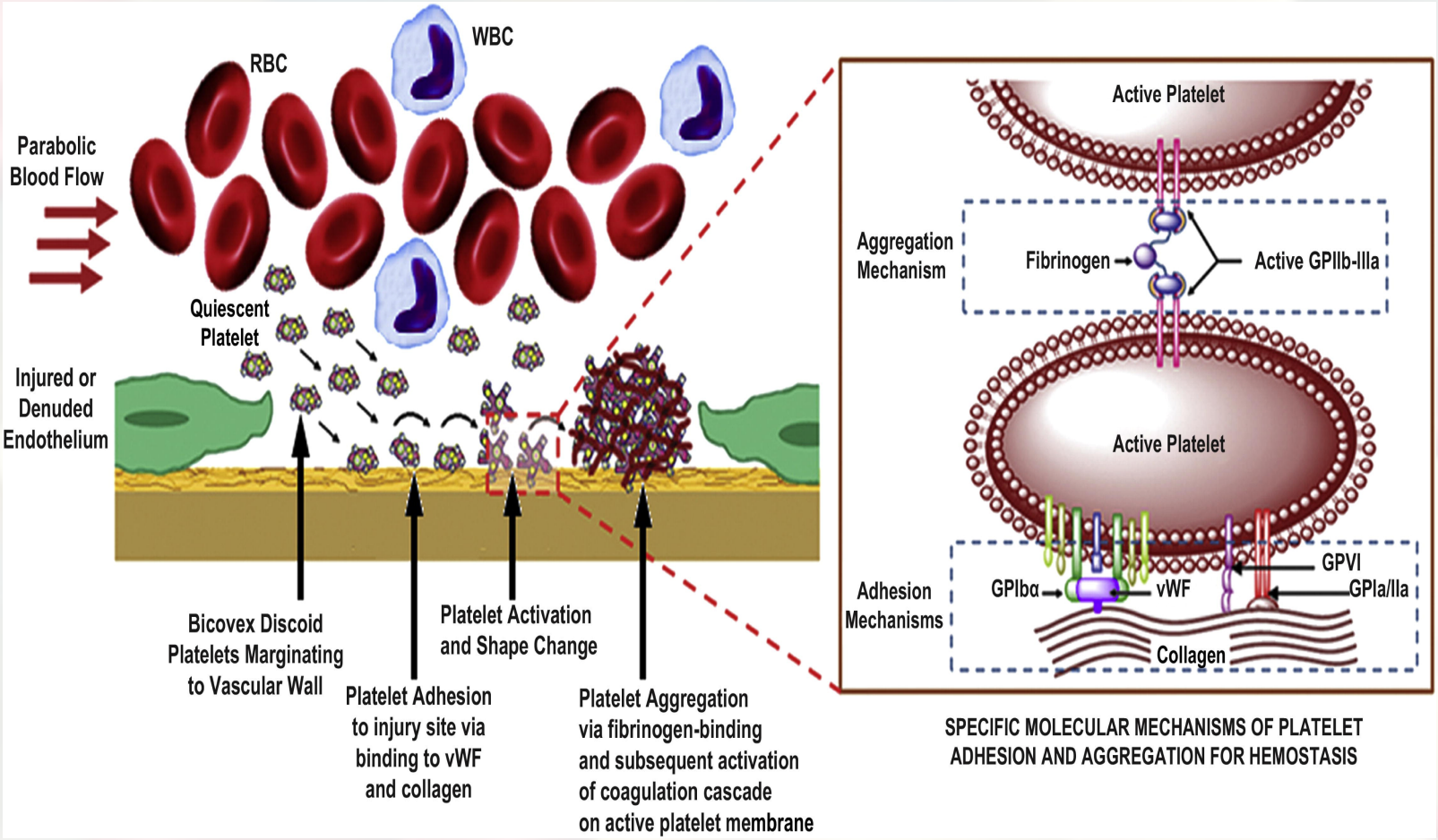
# Platelet Adhesion Mechanism




SPECIFIC MOLECULAR MECHANISMS OF PLATELET ADHESION AND AGGREGATION FOR HEMOSTASIS

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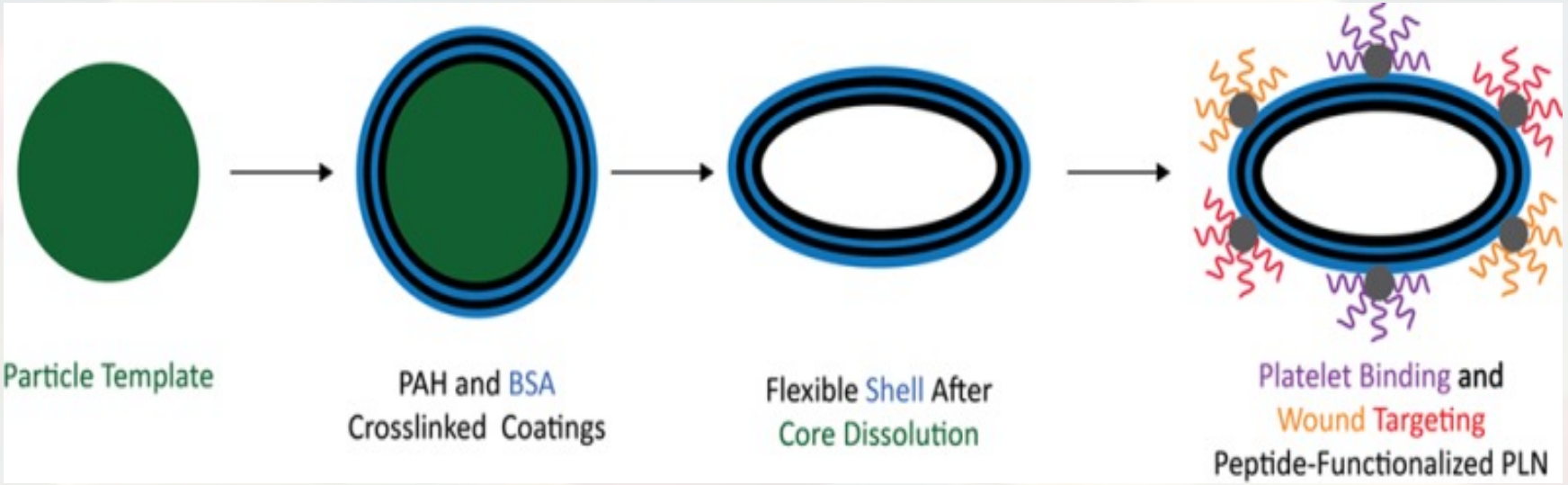
# Synthetic Platelet Mimetics

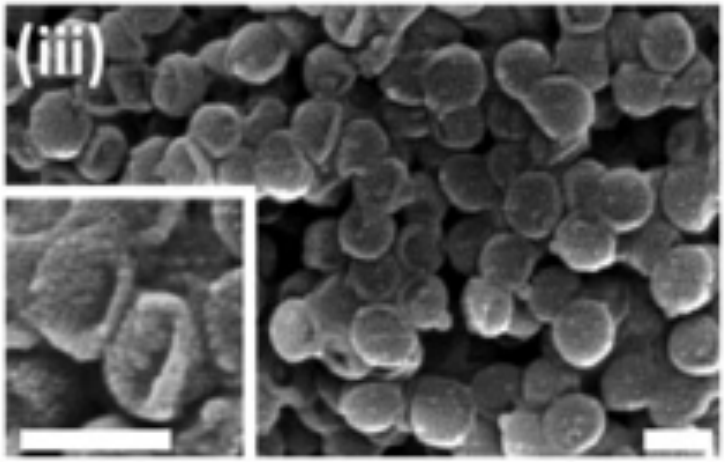



***Flexible shell***

- **Layer-by-layer fabrication**
- **Removal of template / core**

***Functionalization***

- **Peptide ligands**



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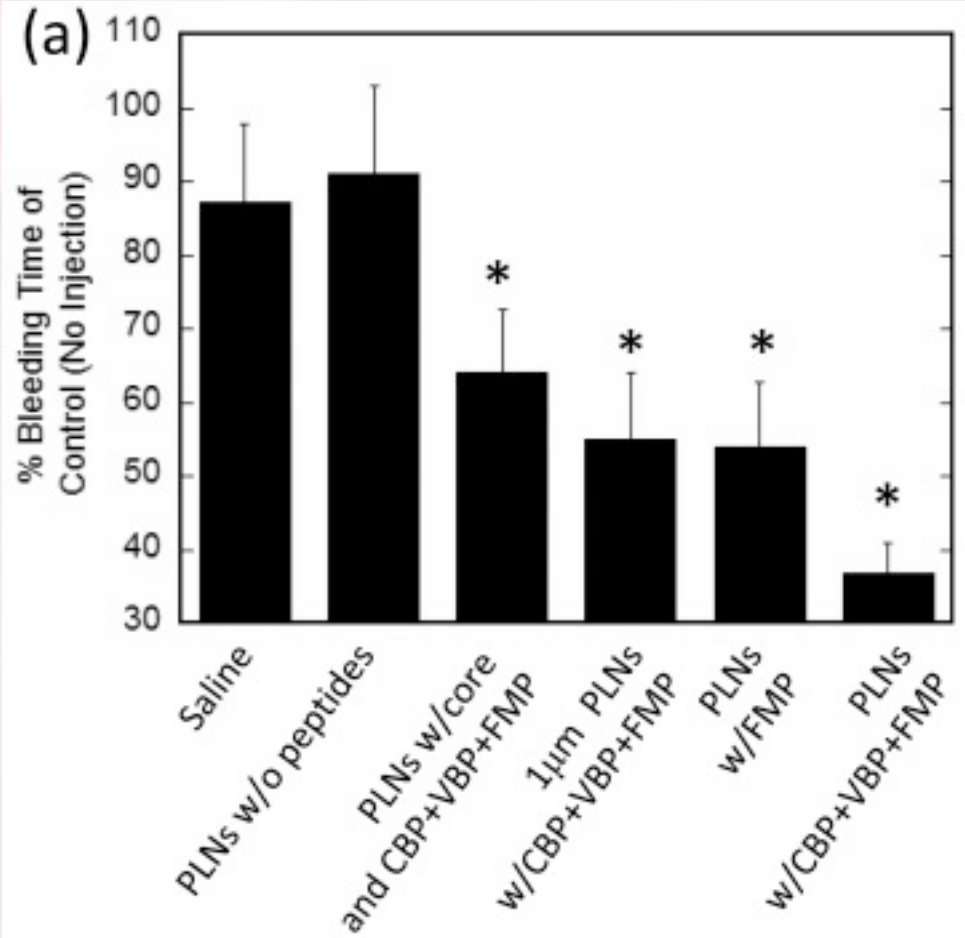


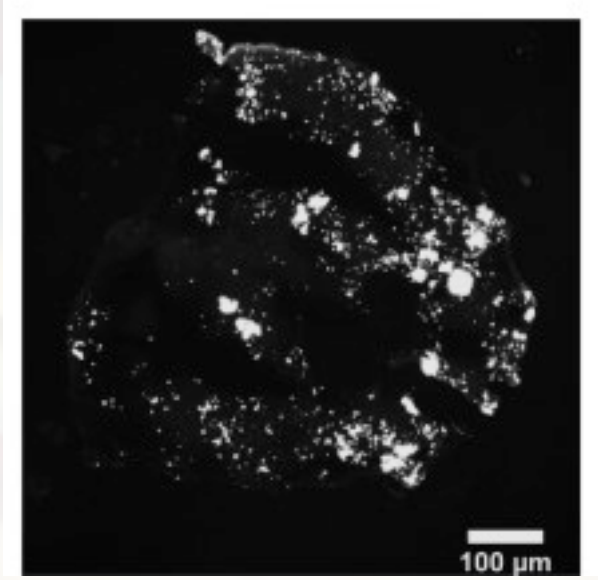

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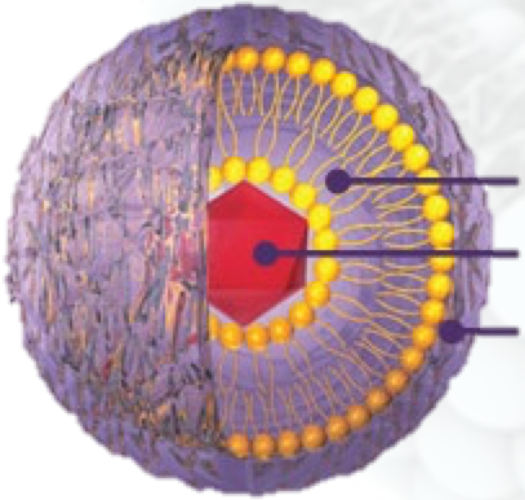
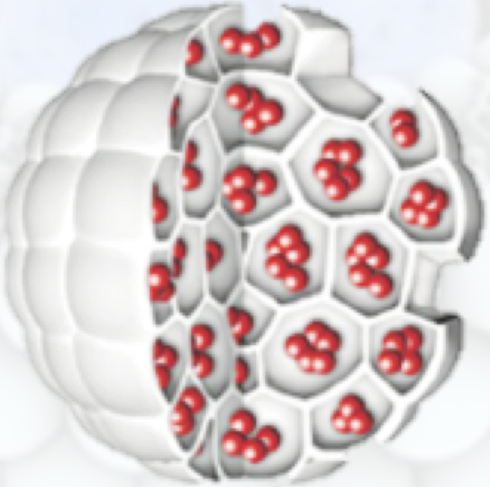
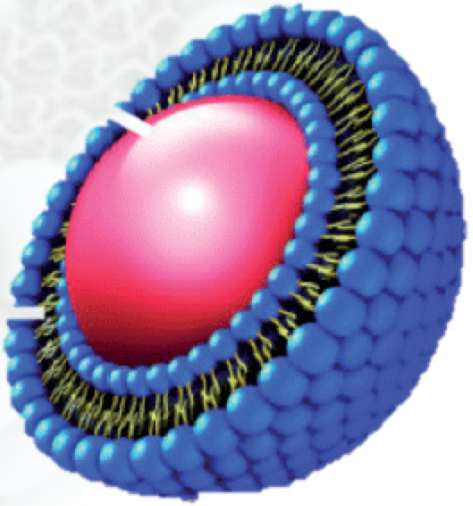
# Drug-filled Liposomes



*Doxil*
Doxorubicin-filled
Stealth Liposome



*DepoCyt*
Cytarabine-filled
Liposome



*DaunoXome*
Daunorubicin-filled
Liposome

**All Single Drug Payloads**

**What about multiple drugs ?**

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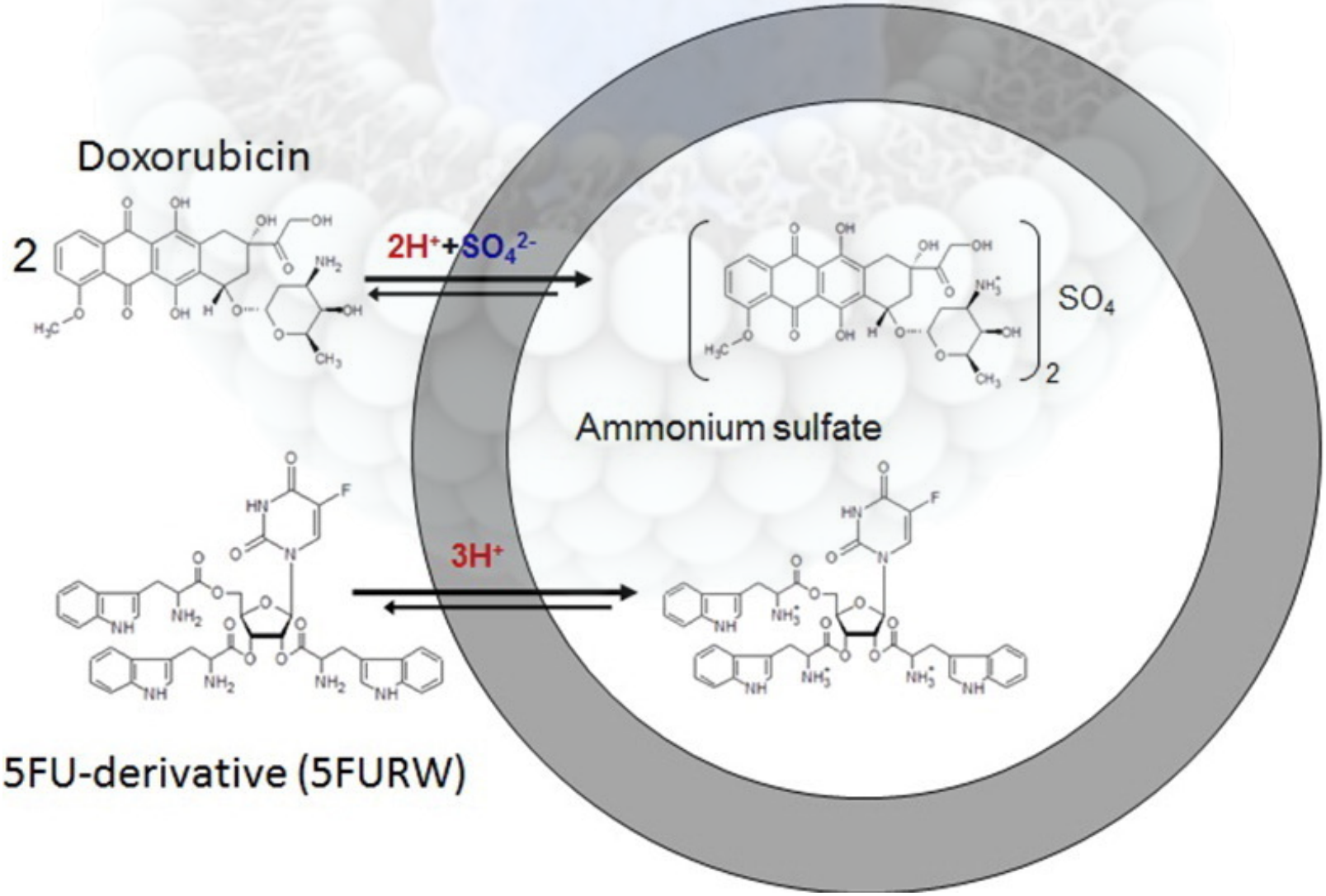
# DAFODIL



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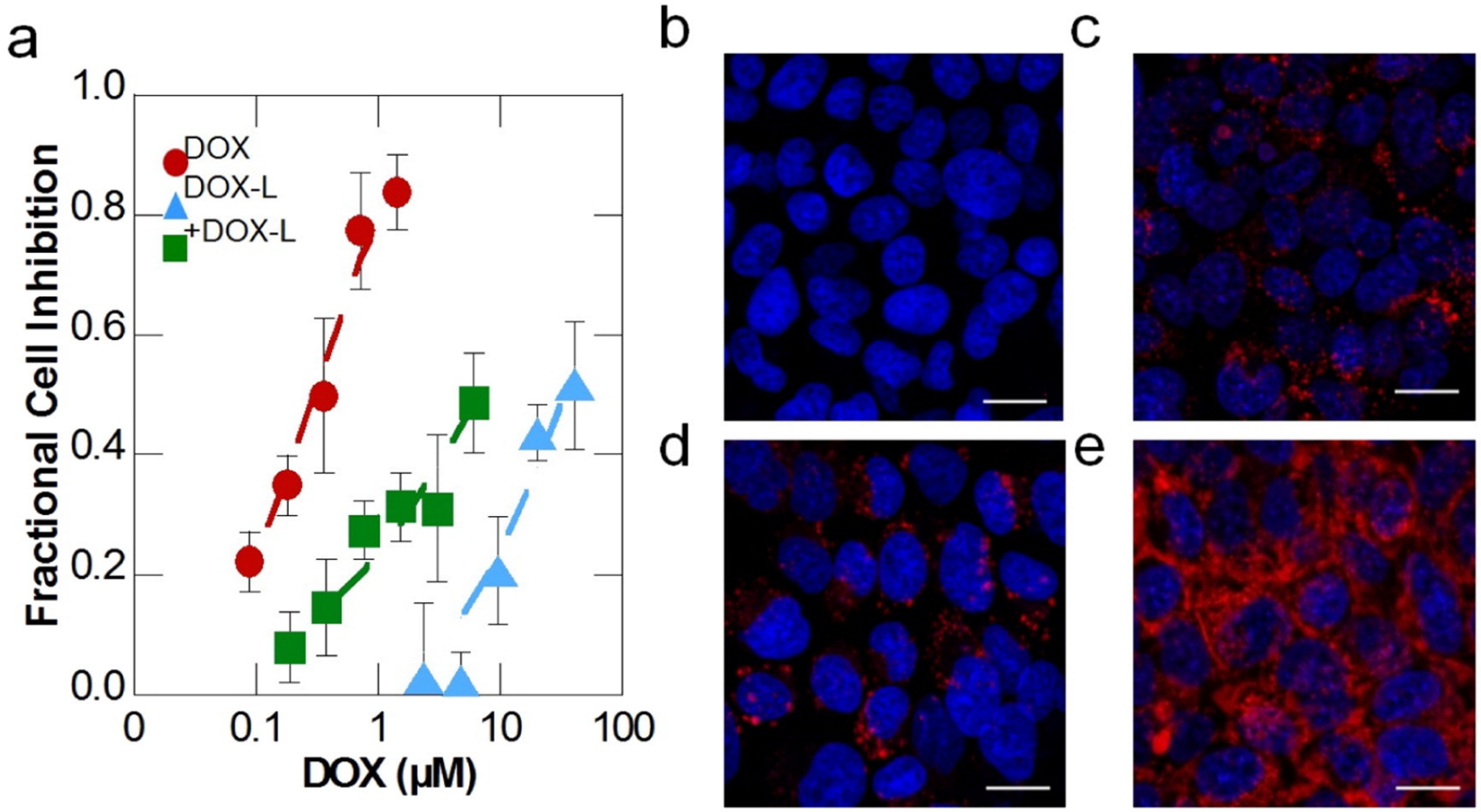
# DAFODIL



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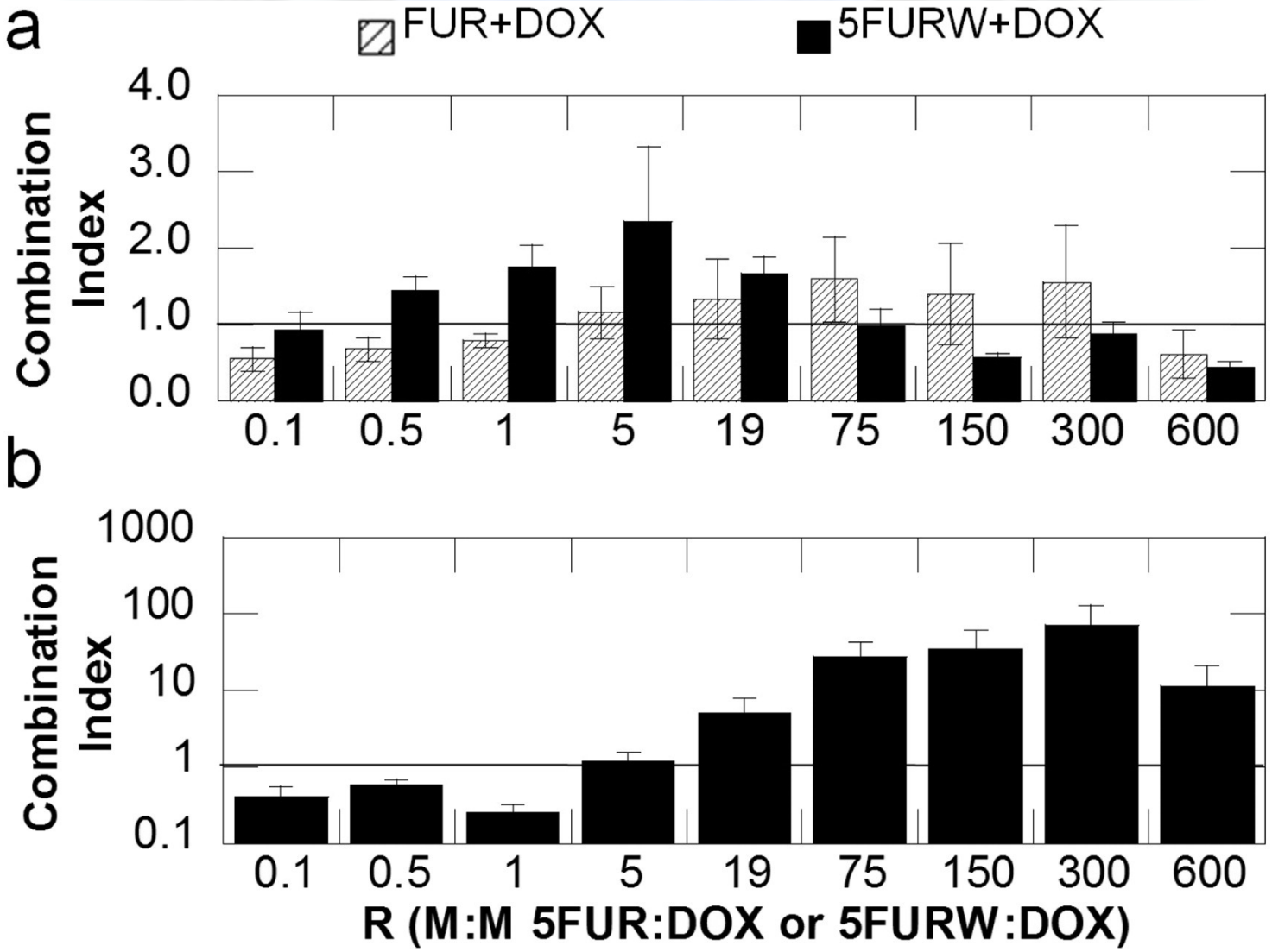

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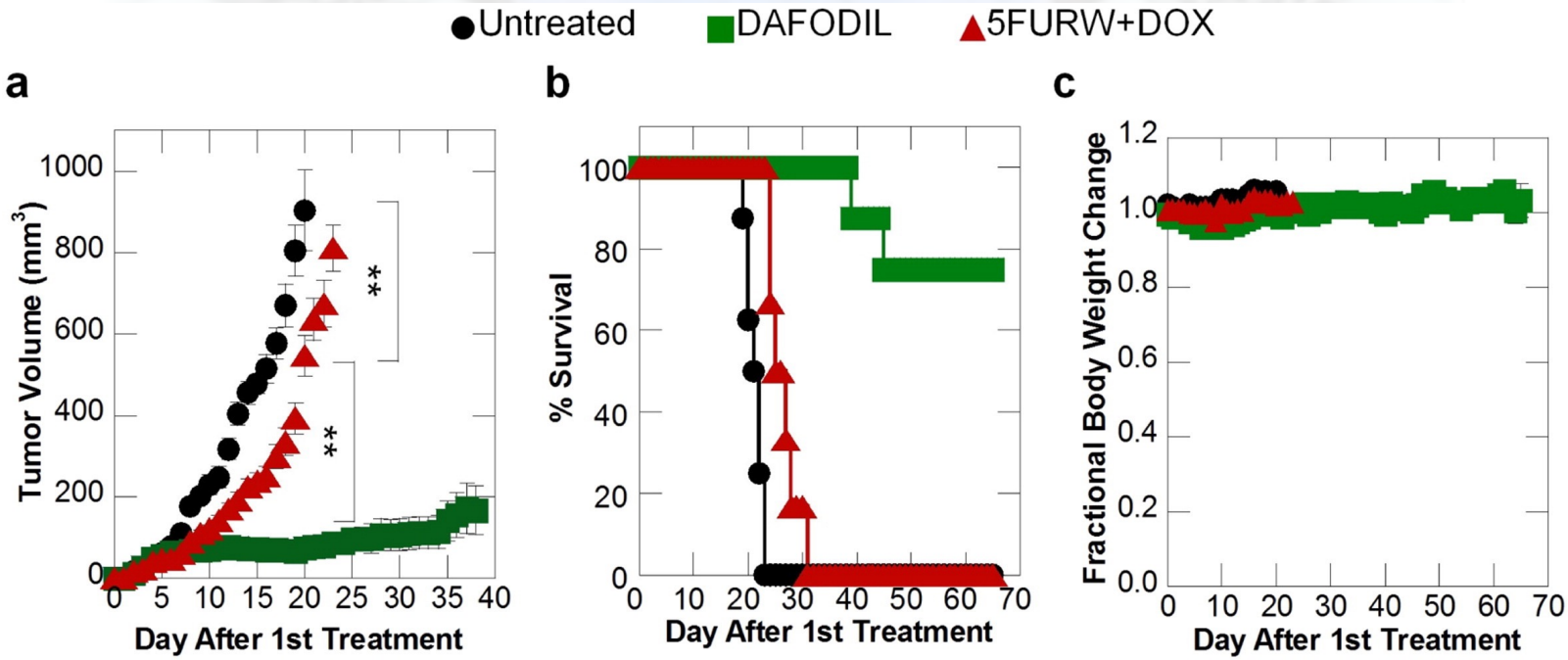

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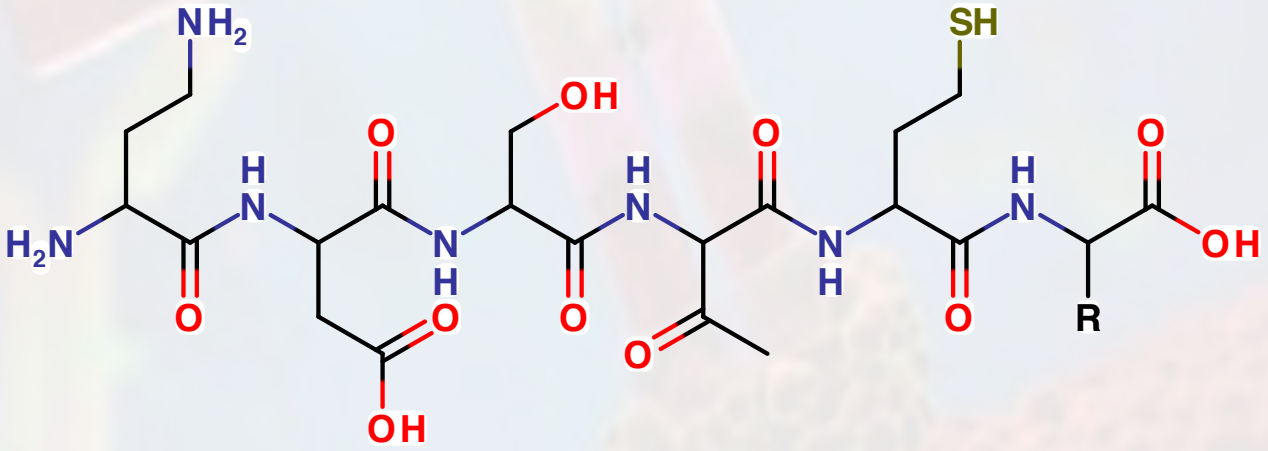
# Peptide-Drug Conjugates

- Controlled stoichiometry (synergy)
- Controlled release (schedule)
- Improved targeting (co-delivery)




Lys Asp Ser Thr Cys E.C.S.

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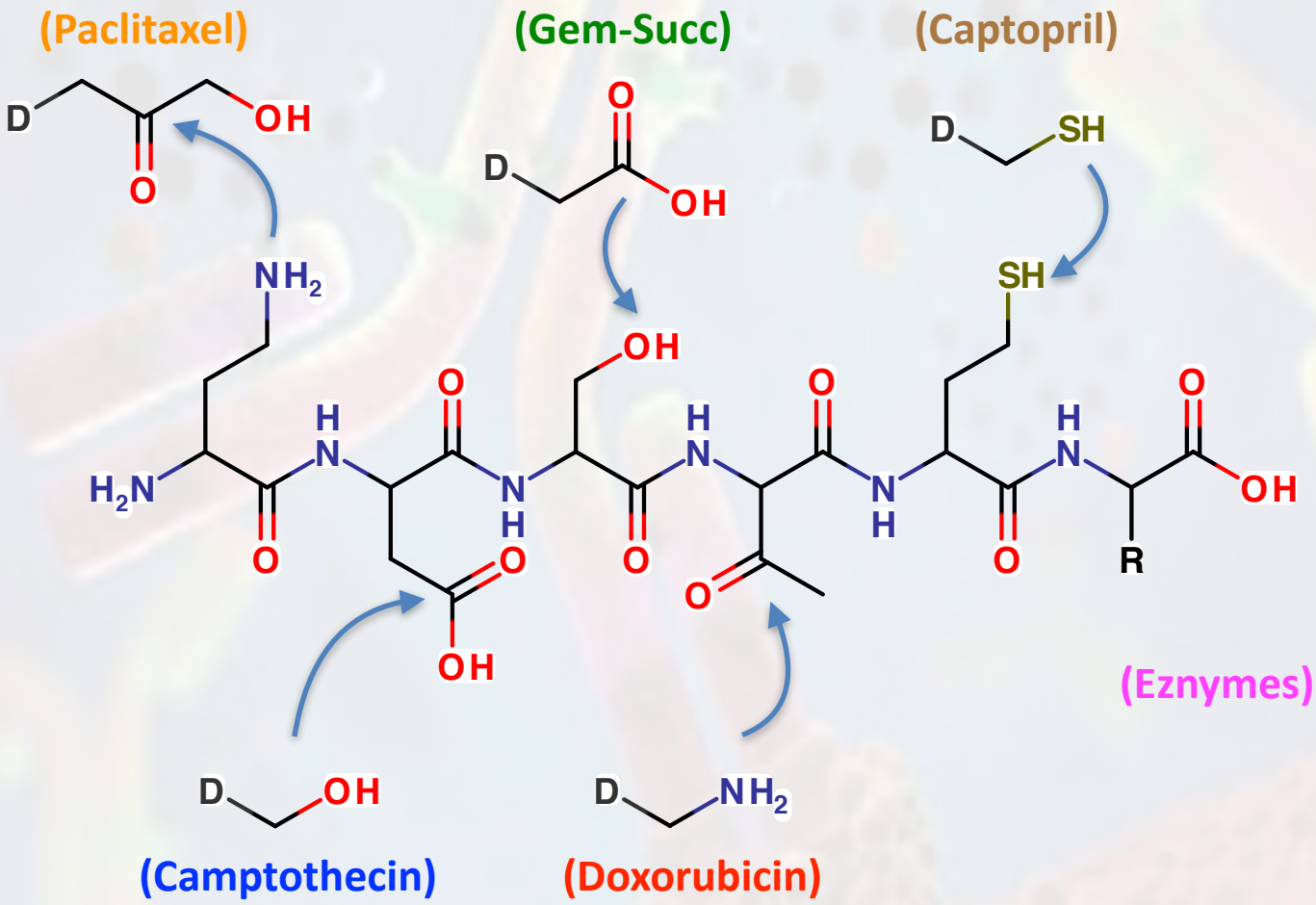
# Peptide-Drug Conjugates



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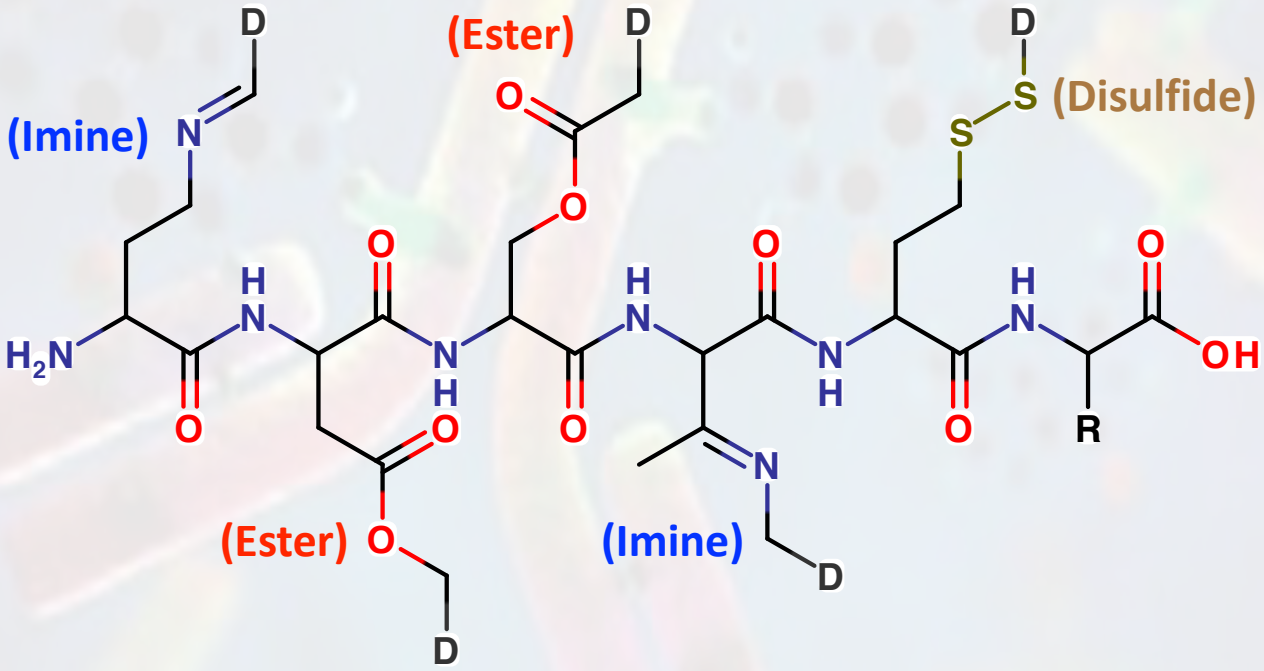
# Peptide-Drug Conjugates




- Controlled stoichiometry with AA sequence
- Controlled release with cleavable bonds
- Improved targeting, it's one molecule

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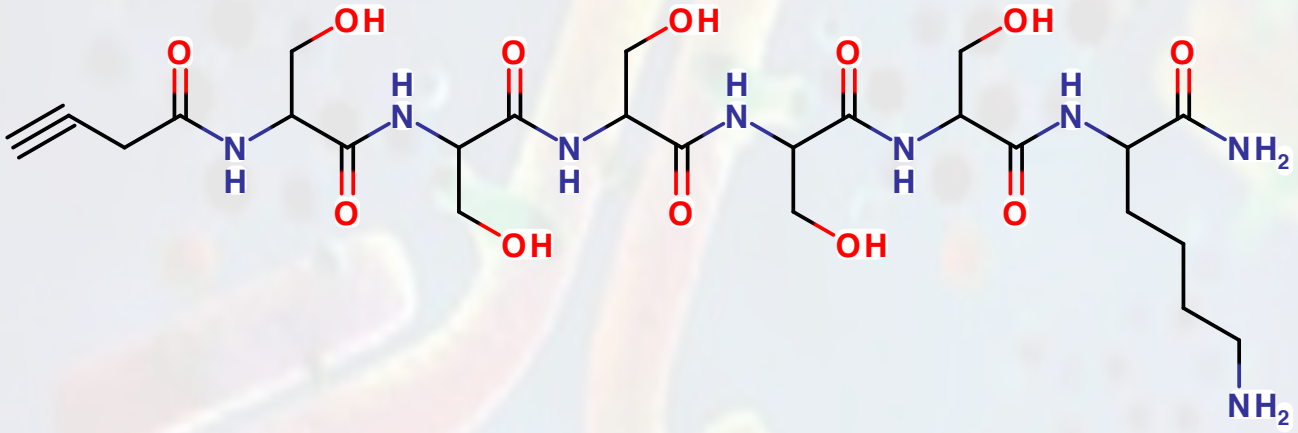
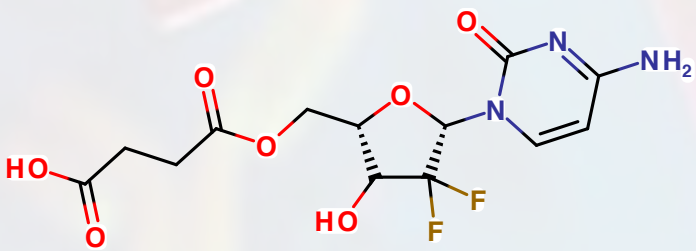
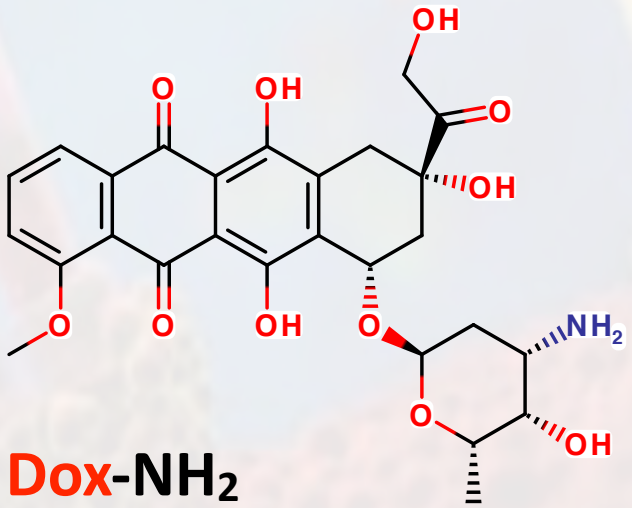
# DNA-Peptide-Drug Conjugates





GEM-COOH



Dox-$NH_2$

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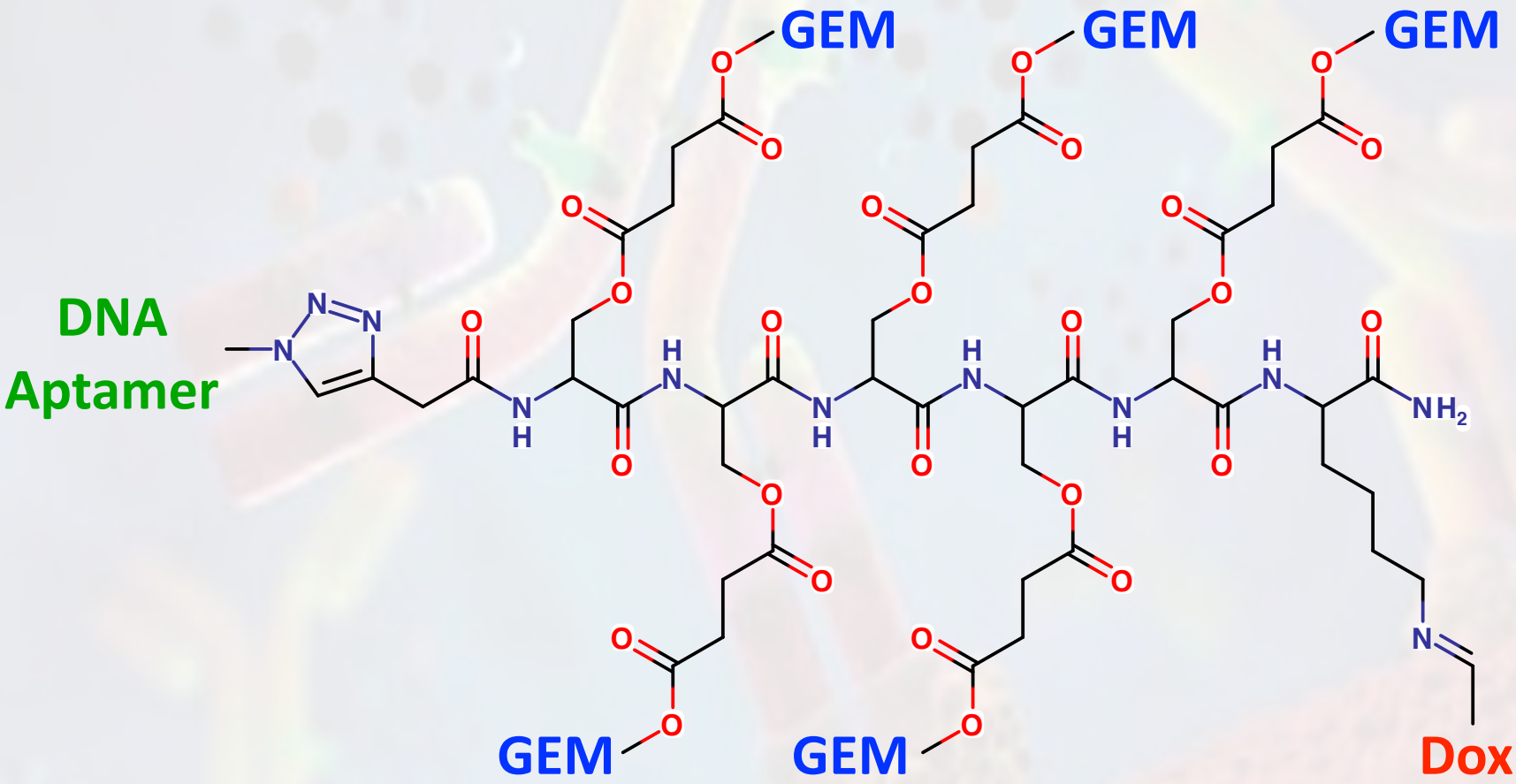
# DNA-Peptide-Drug Conjugates



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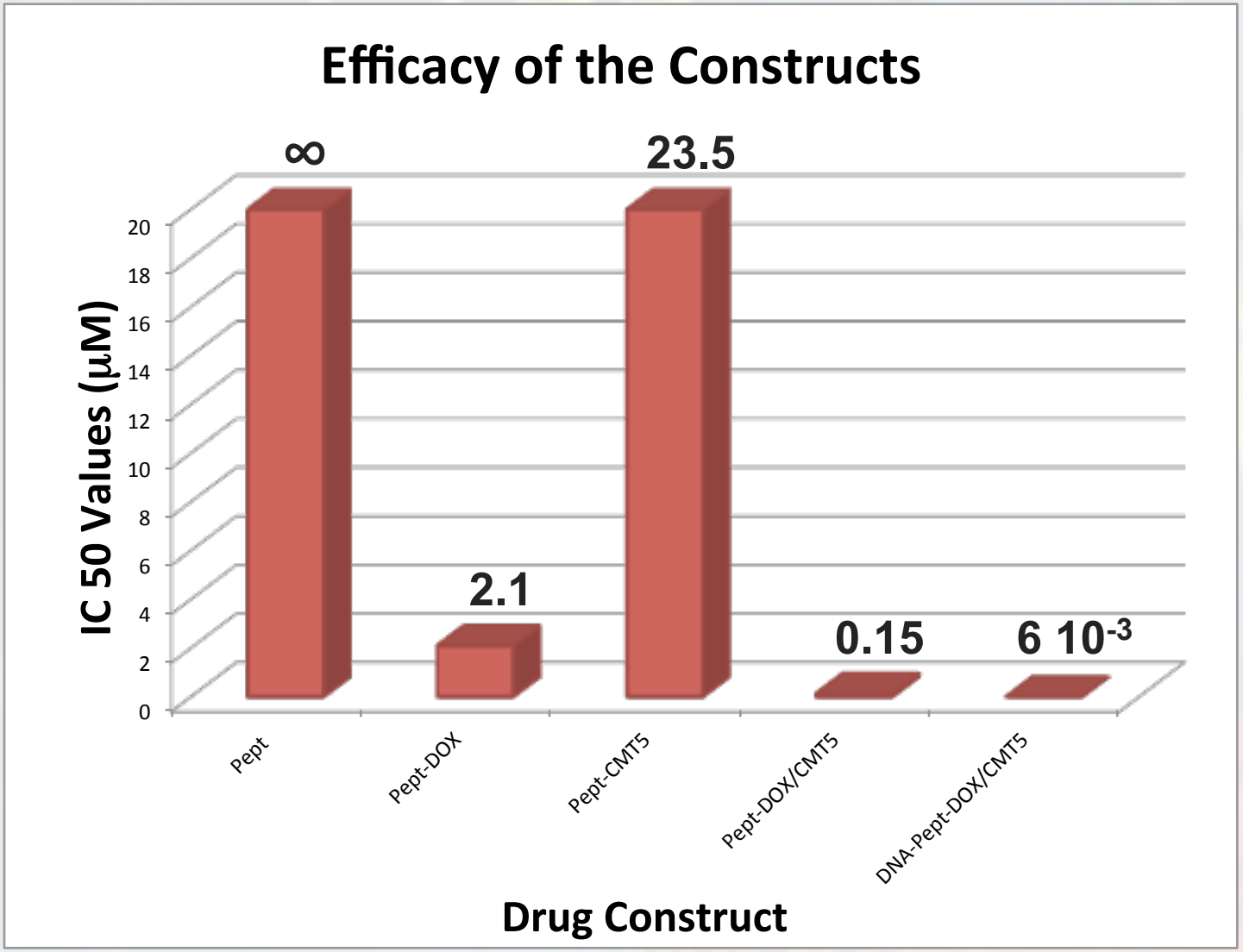

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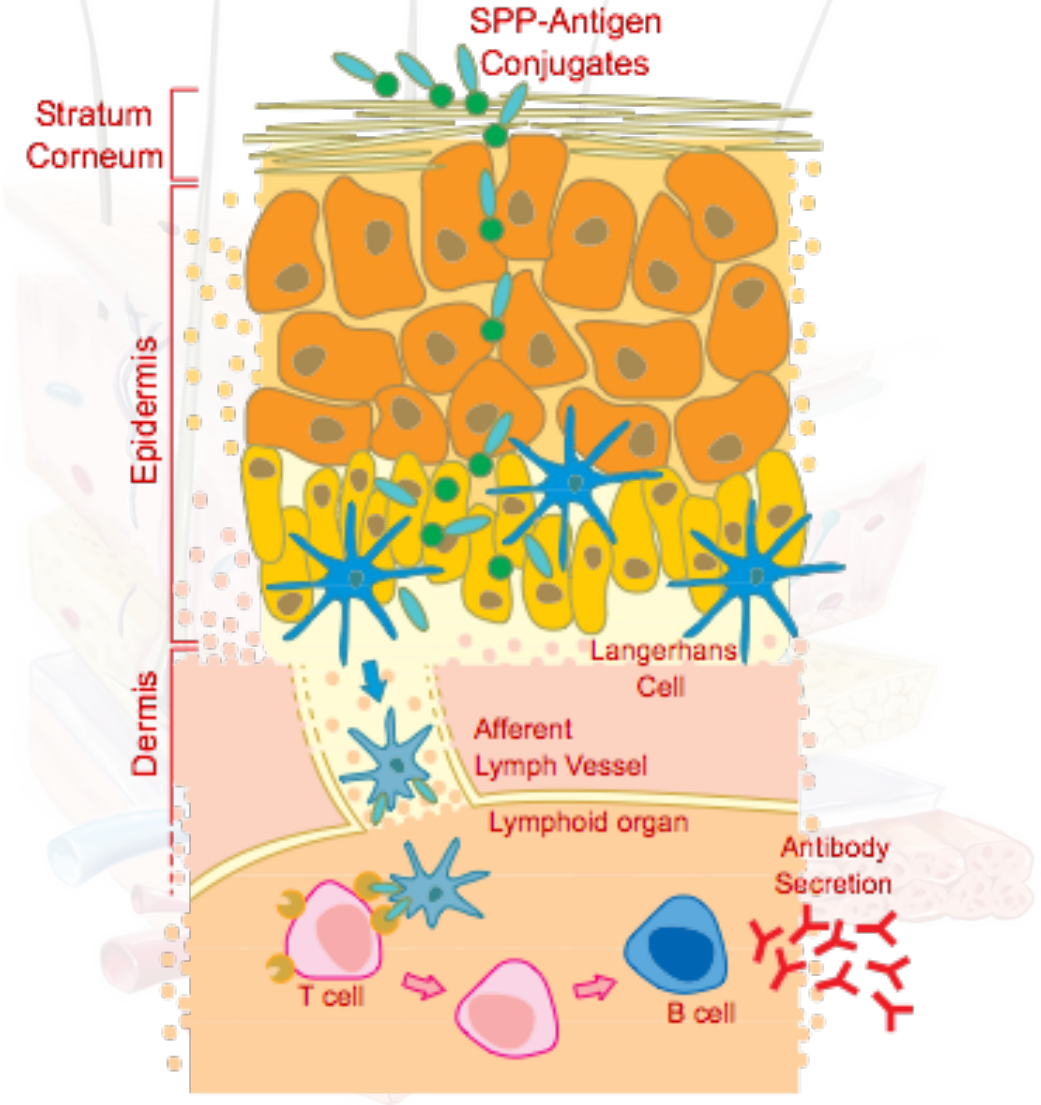
# Skin-Permeating Peptides (SPPs)



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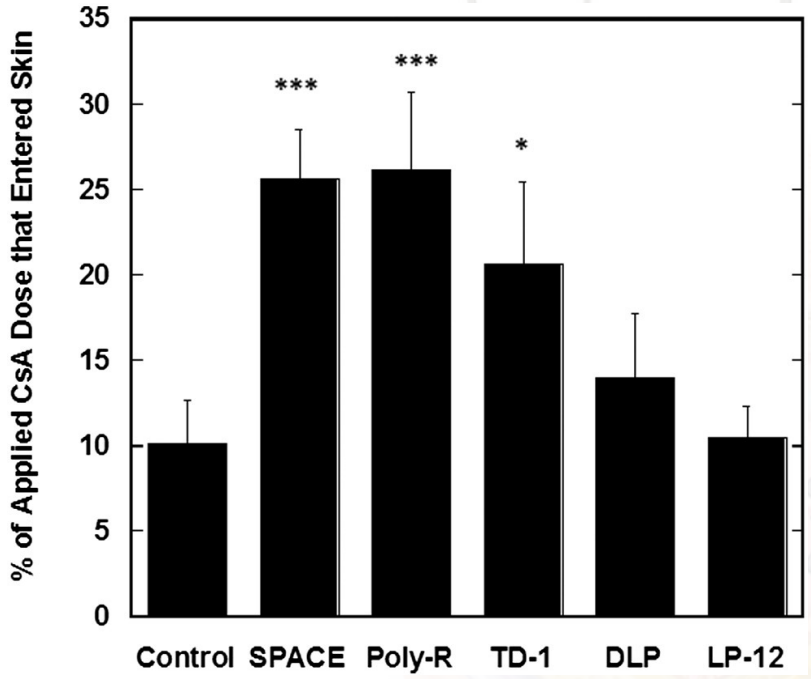


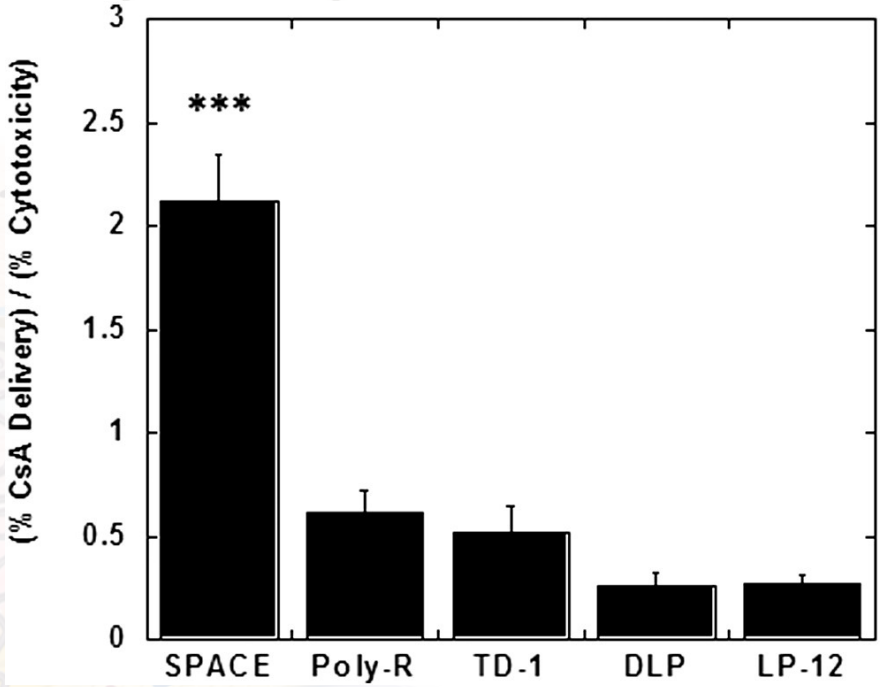

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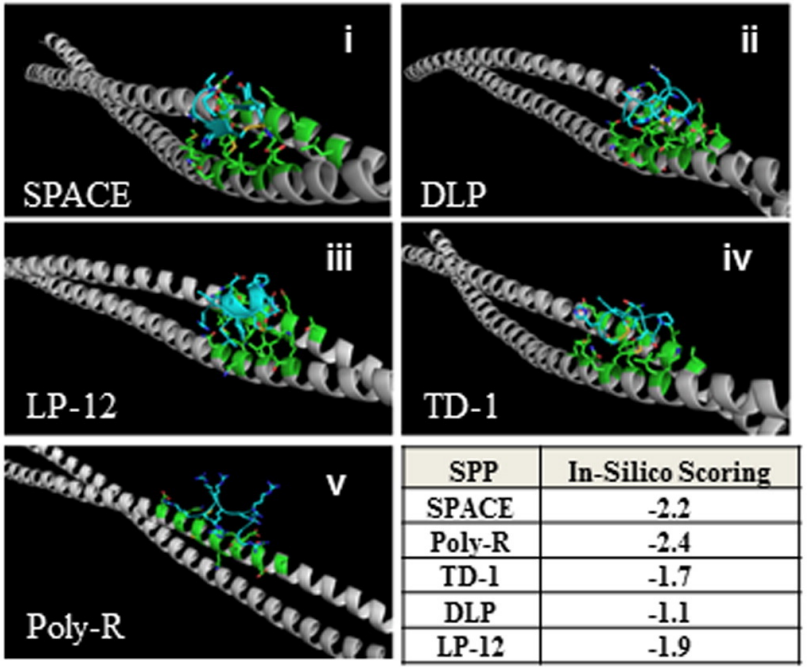
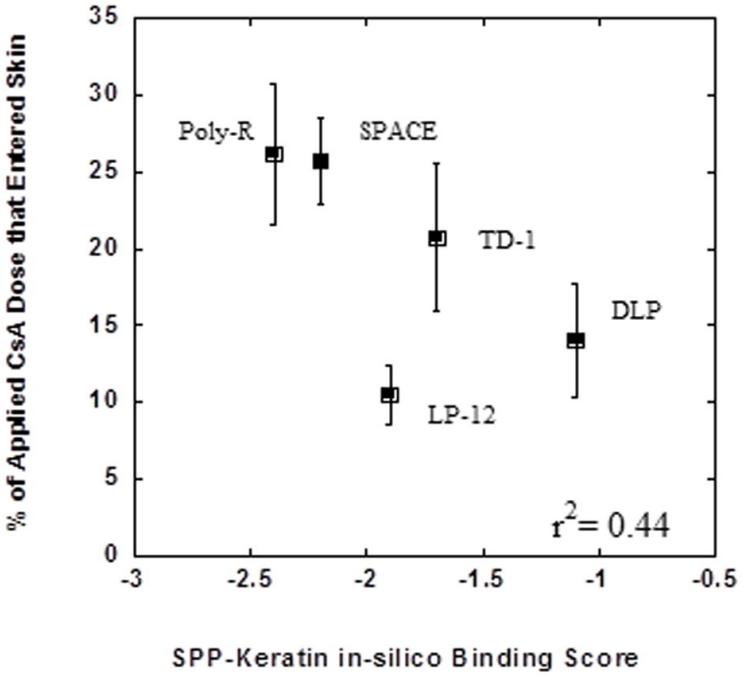
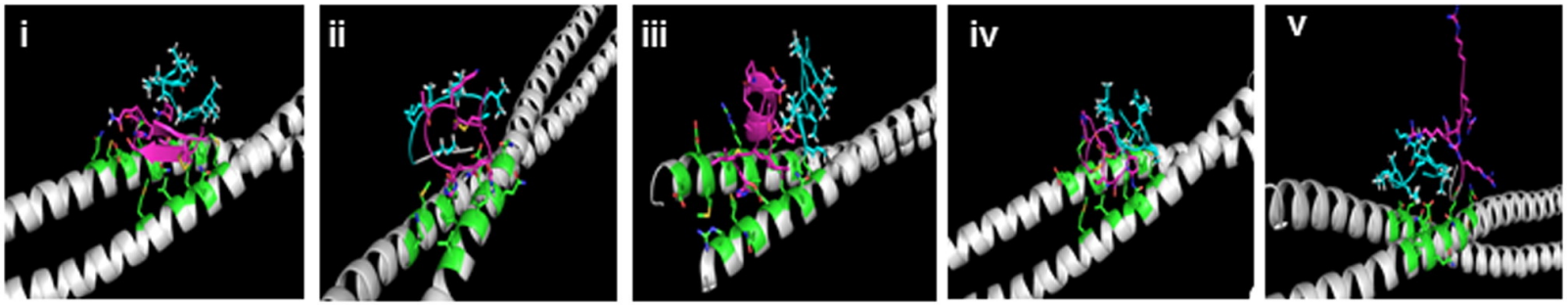



| SPP | In-Silico Scoring |
|---|---|
| SPACE | -2.2 |
| Poly-R | -2.4 |
| TD-1 | -1.7 |
| DLP | -1.1 |
| LP-12 | -1.9 |



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# Finding new SPPs

| | |
|---|---|
| Assign AAs to be included in the library | 10 |
| Assign sequence length | 8 |
| Theoretical library diversity | $10^8$ |
| Assign AA(s) in fixed positions | |
| Max. number of an AA per sequence | |
| Mutual exclusion of AAs per sequence | |
| Min. number of different AAs per sequence | |
| Max. number of the same AA in a row | |
| Max. number of similar AAs per sequence | |
| Final library diversity | ~ 1000 |

**Library generated with a Pymol Script**

**Library screened with HADDOCK**

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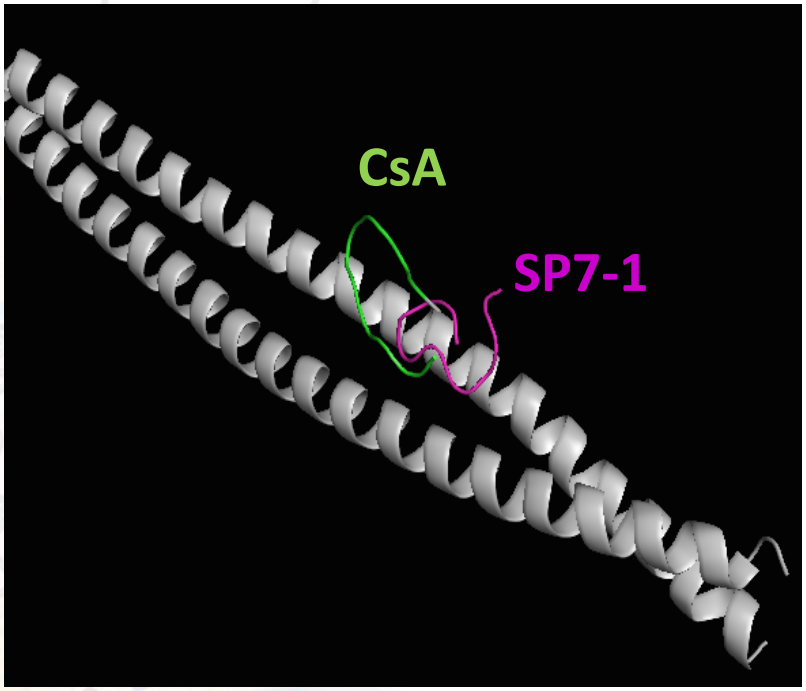
# Finding new SPPs

| SPP ID | Sequence |
|---|---|
| SP7-1 | ACSATLQHSCG |
| SP7-2 | ACSLTVNWNCG |
| SP7-3 | ACLSVNHNACG |
| SPACE™ | ACTGSTQHQCG |
| SP7-5 | ACSASTNHNCG |
| SP7-4 | ACTSTGRNACG |
| SP 6 | ACSASTNGCG |
| SP 8 | ACNAHQARSTCG |



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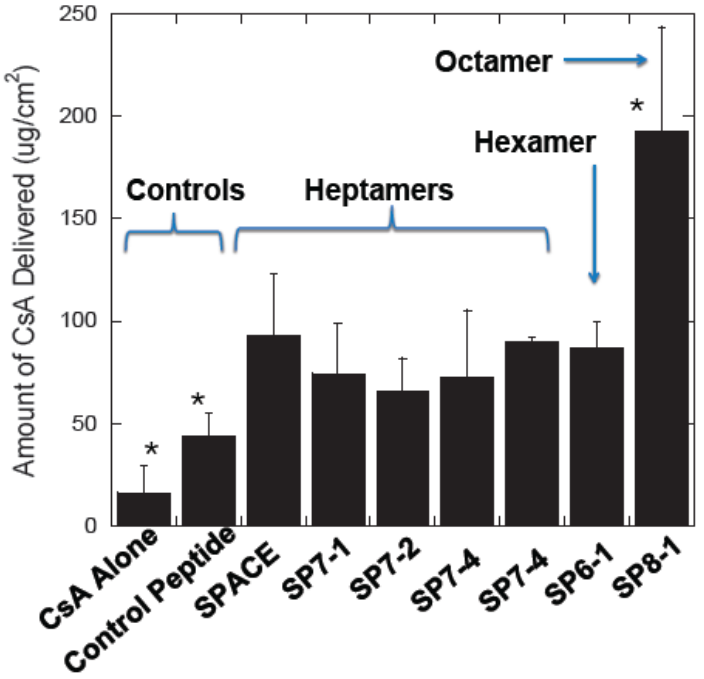
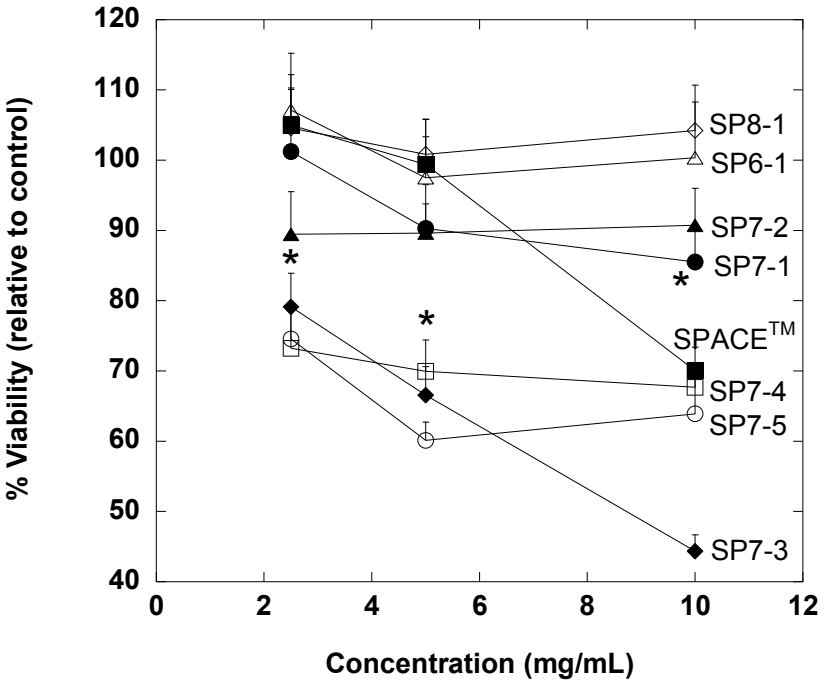
# New SPPs

| SPP ID | Sequence | SC+ Epidermis | Dermis | Receptor |
|---|---|---|---|---|
| SP7-1 | ACSATLQHSCG | 819.2 ± 62.2 | 149.7 ± 5.6 | 42.4 ± 8.5 |
| SP7-2 | ACSLTVNWNCG | 774.0 ± 110.2 | 166.7 ± 45.2 | 65.0 ± 14.1 |
| SP7-3 | ACLSVNHNACG | 759.9 ± 73.4 | 39.5 ± 25.4 | 16.9 ± 11.3 |
| SPACE™ | ACTGSTQHQCG | 545.2 ± 79.1 | 53.7 ± 31.1 | 19.8 ± 19.8 |
| SP7-5 | ACSASTNHNCG | 759.9 ± 62.1 | 124.3 ± 28.2 | 39.5 ± 8.5 |
| SP7-4 | ACTSTGRNACG | 782.5 ± 84.7 | 200.6 ± 59.3 | 96.0 ± 31.1 |



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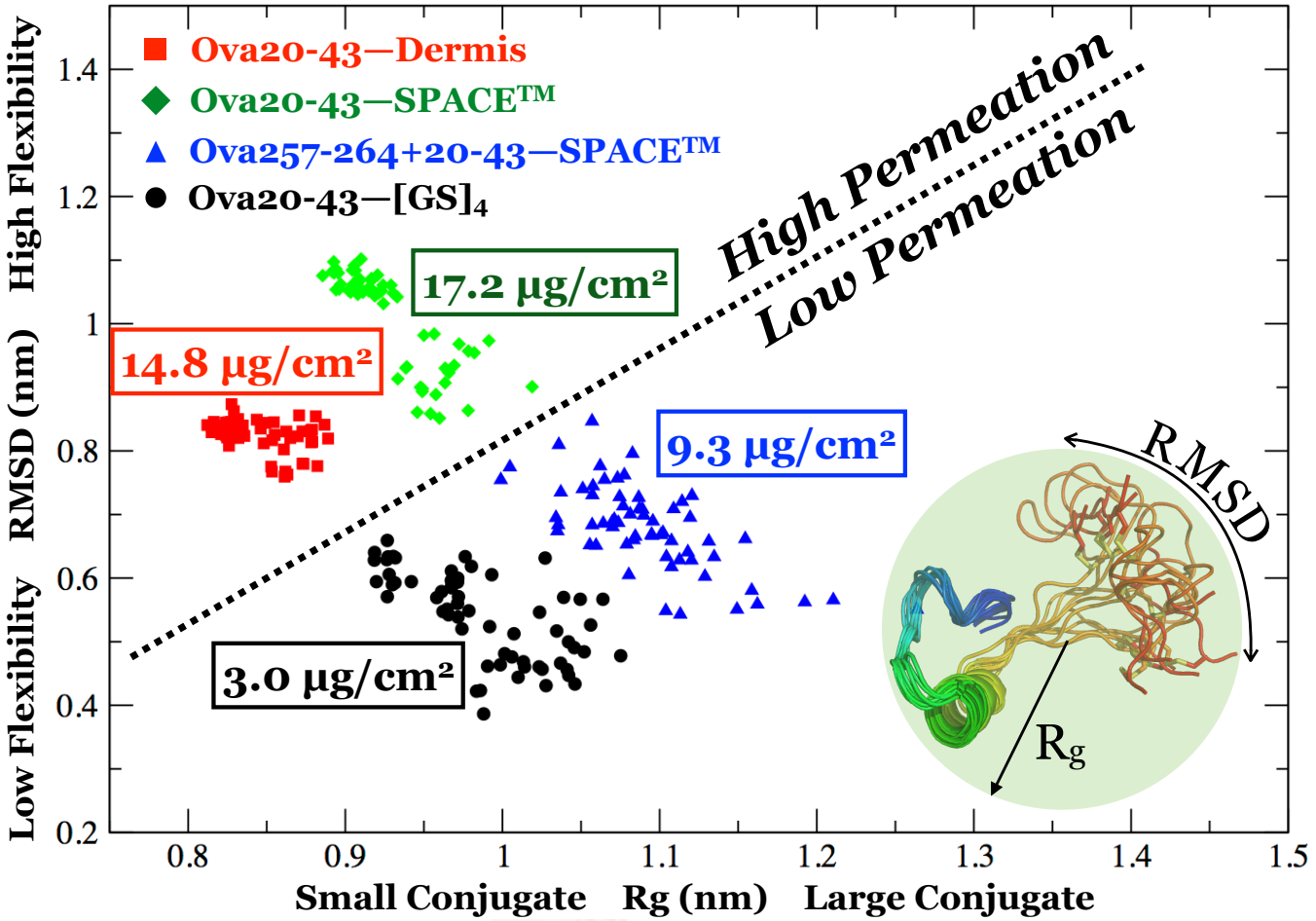
# SPP-Antigen Permeation

## Epidermal penetration



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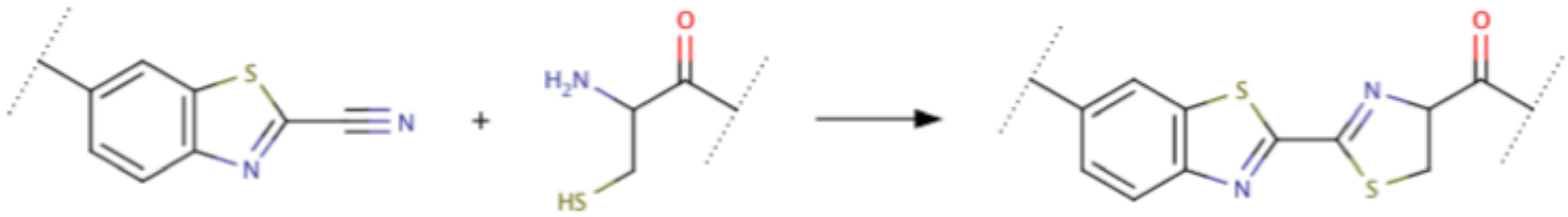
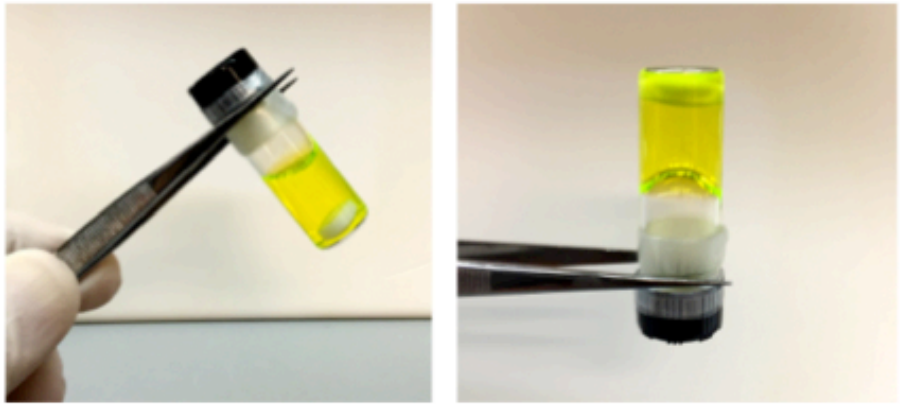
# Self-Gelling Subcutaneous Formulation

(a)




(b)



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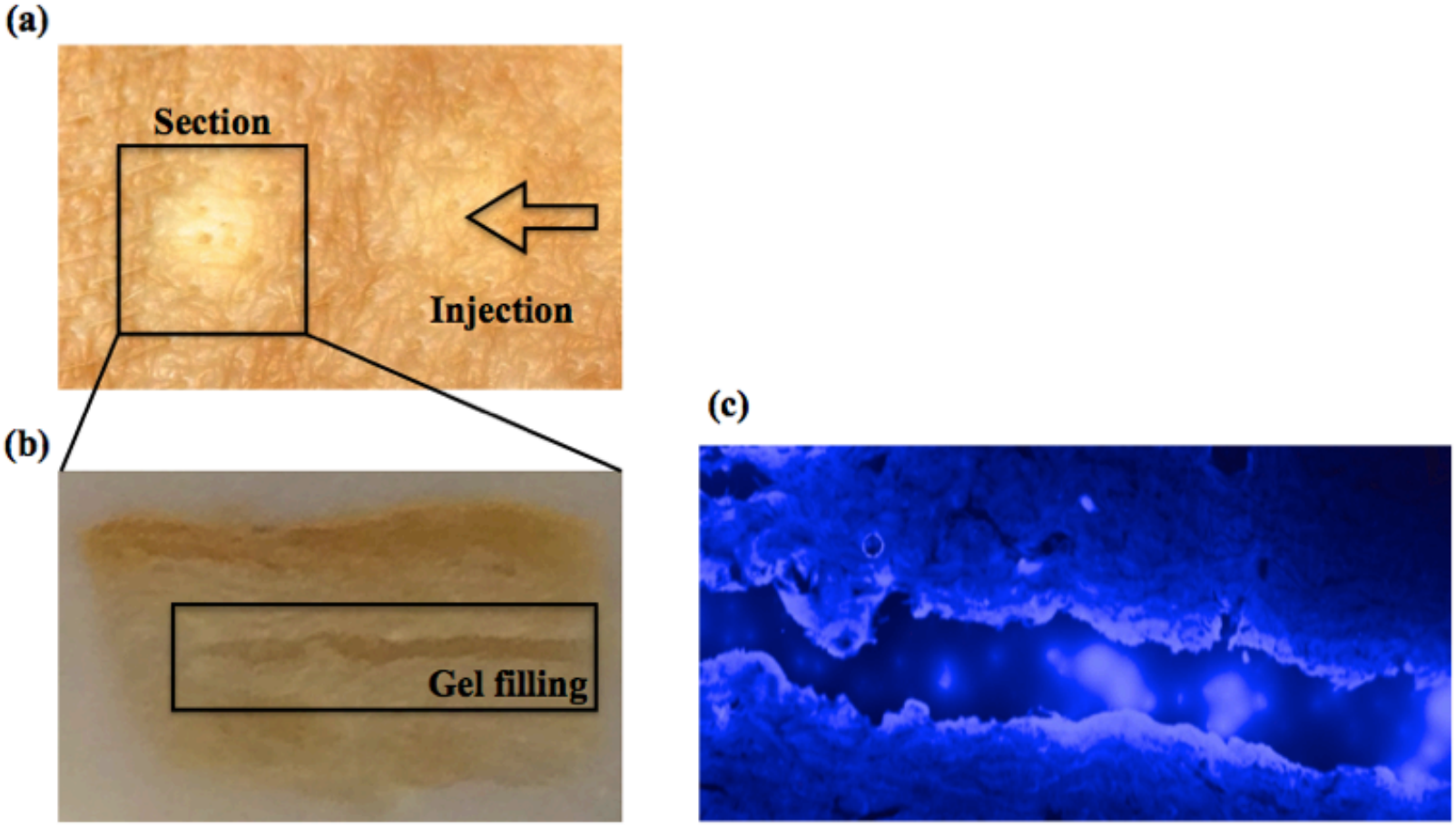
# Self-Gelling Subcutaneous Formulation



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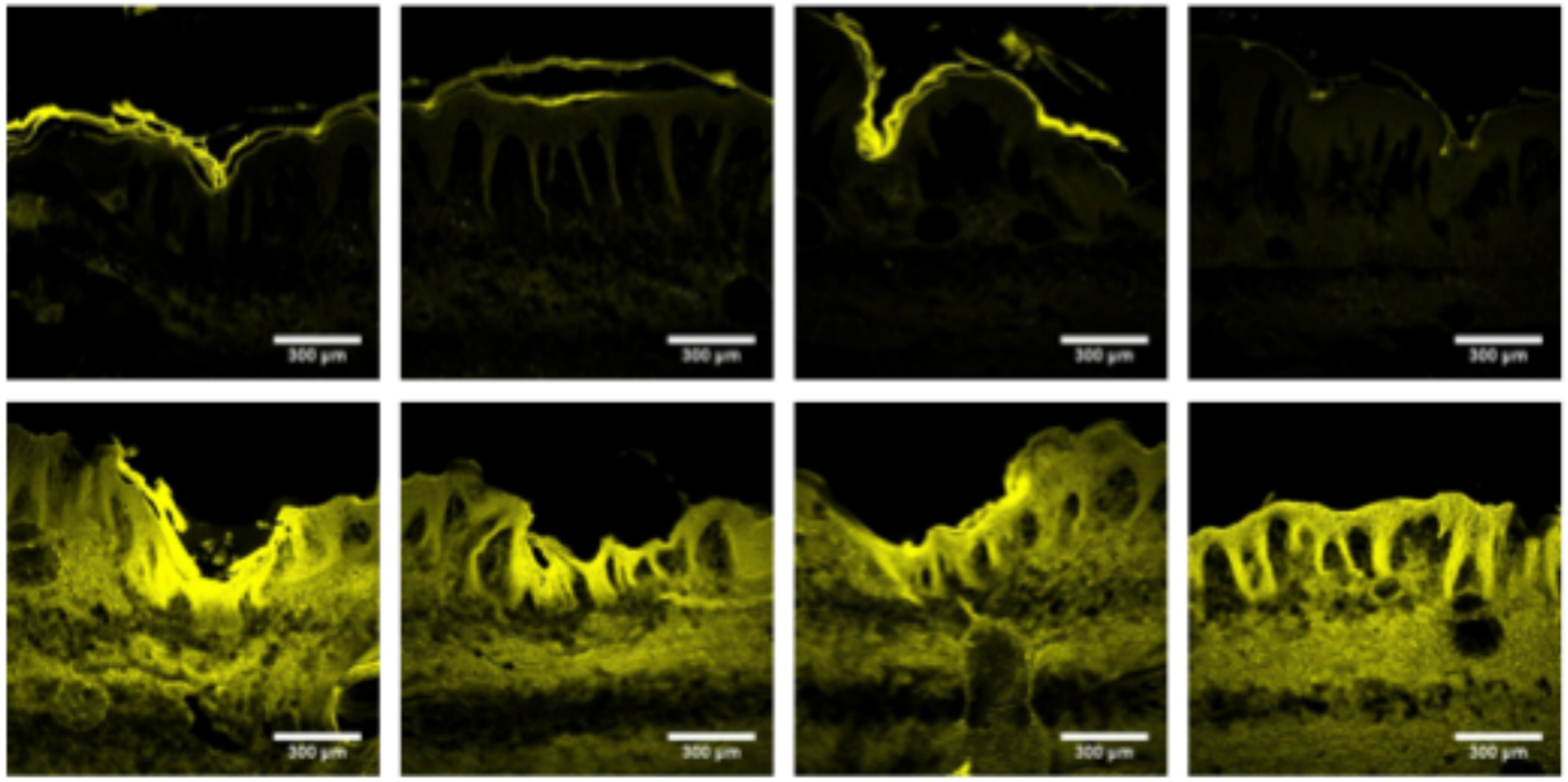

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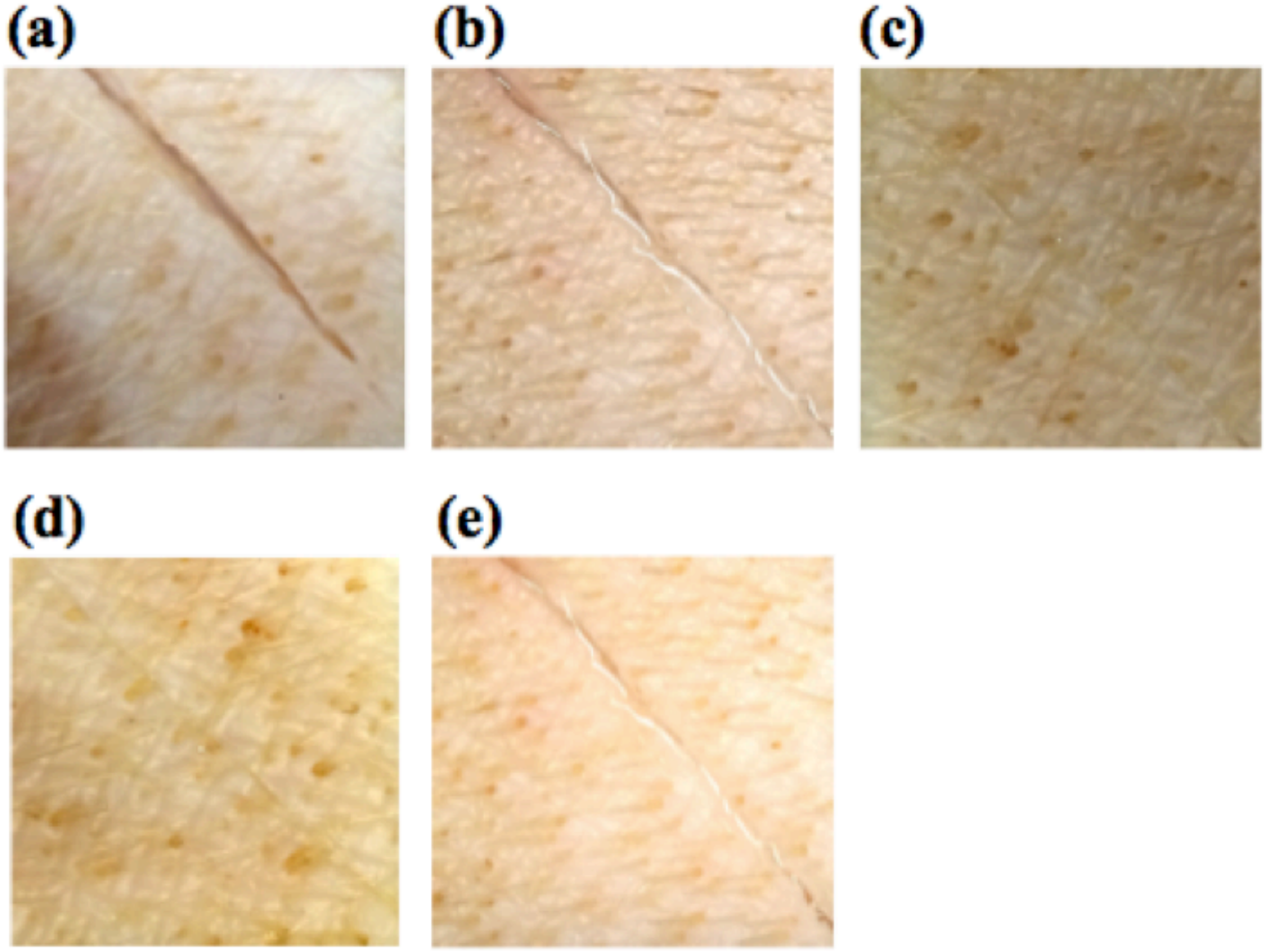

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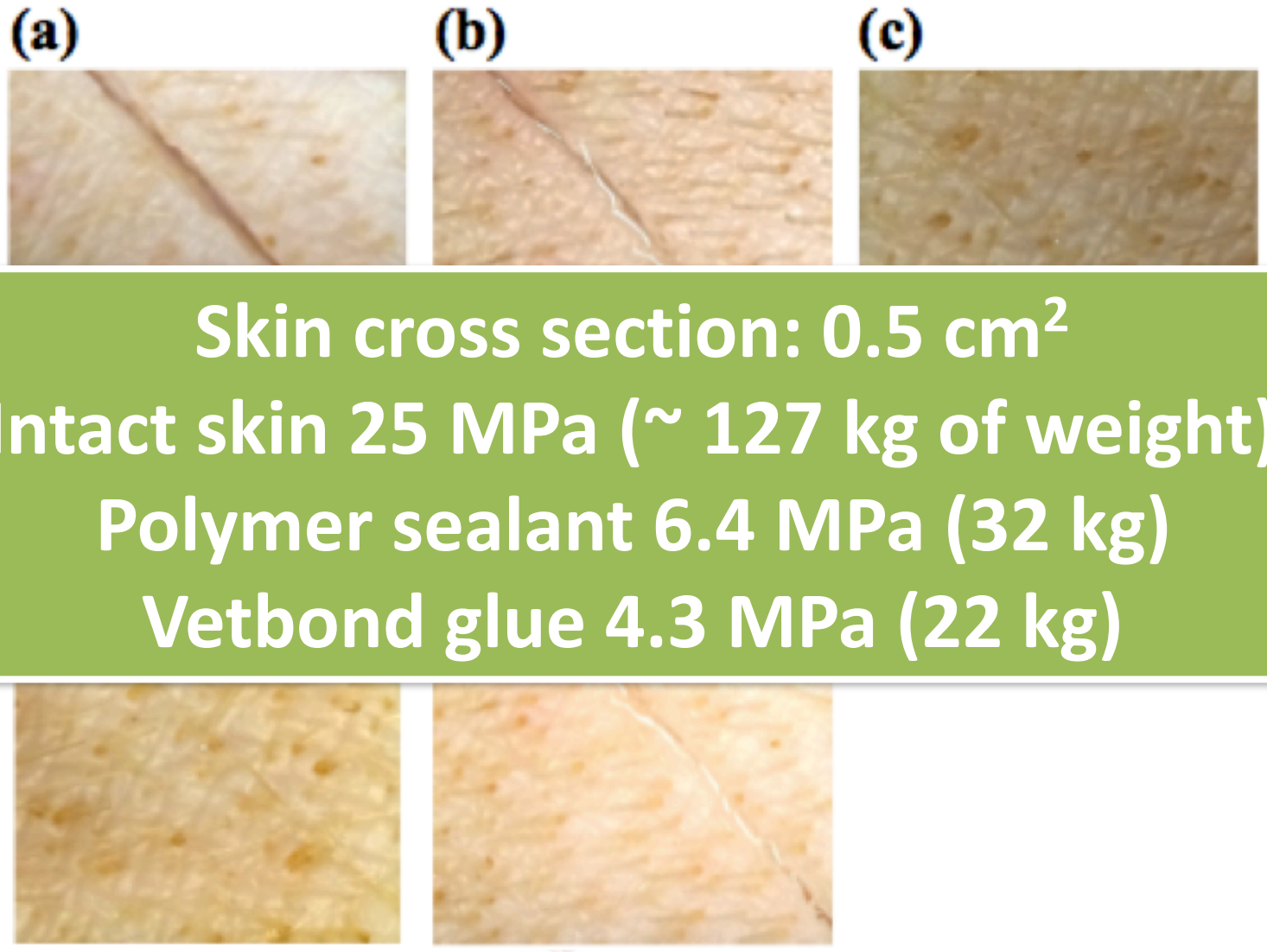


Skin cross section: 0.5 $cm^2$

Intact skin 25 MPa (~ 127 kg of weight)

Polymer sealant 6.4 MPa (32 kg)

Vetbond glue 4.3 MPa (22 kg)

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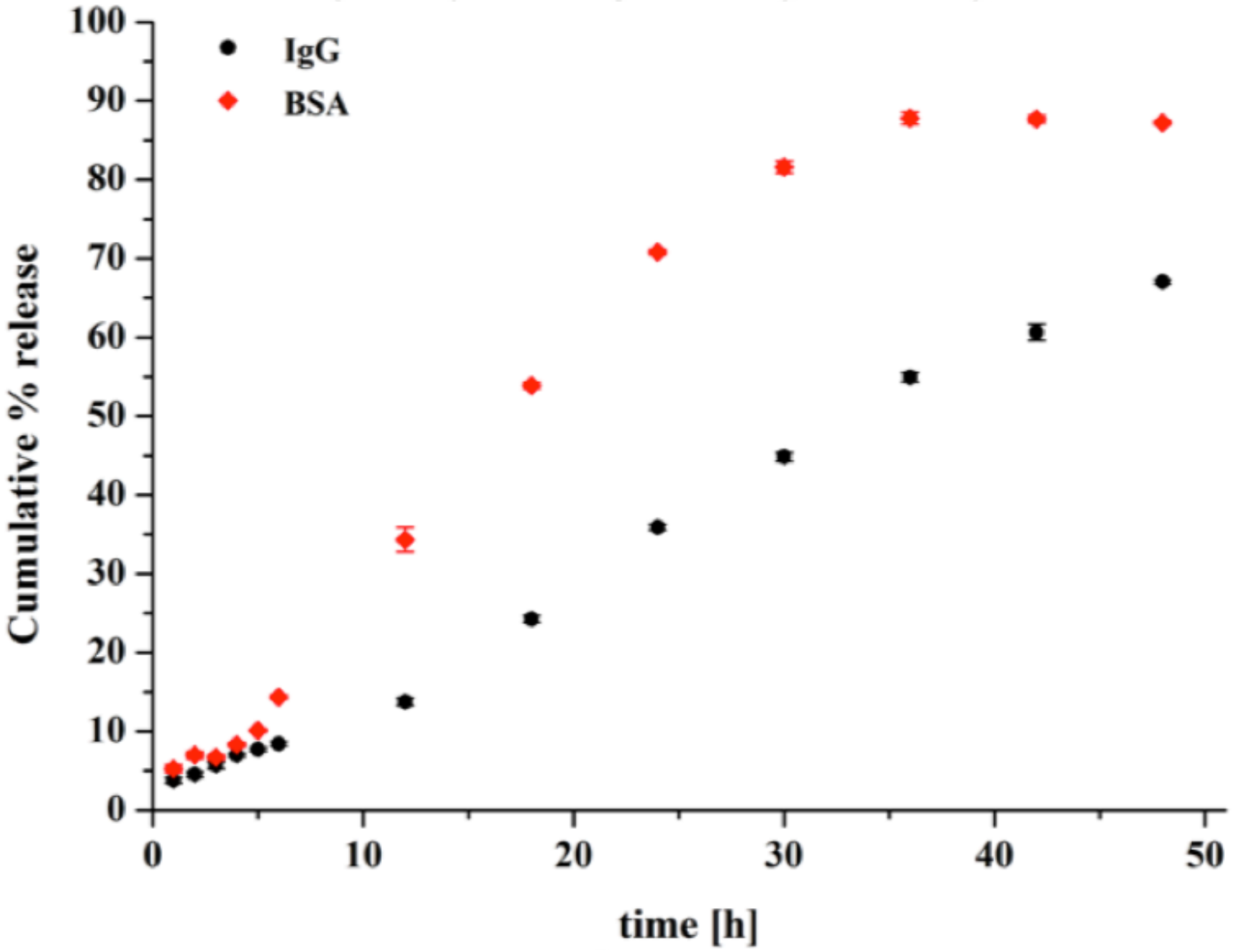
# Self-Gelling Subcutaneous Formulation



# Current research topics

# What's cooking?

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# Current research topics

*Bioseparations*

- T- and light-responsive peptides
- Multi-constrained peptides / peptoids
- Renewable sensors

*Drug delivery*

- Field-controlled scheduled delivery
- Novel substrates for drug coupling

*Material science*

- Peptoid mimetics of stimuli-responsive polymers

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# Questions ?

kalilak