Woudschoten, November 2025

Academy Toegepaste Biowetenschappen en chemie

Chemistry and Biology
→ Fruitfull marriage

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OF APPLIED SCIENCES

About me;

Nanda Smits

Docent Chemie HAN

- Studentbegeleiding en Coaching
- Stage-/afstudeerbegeleiding
- Theorievakken (vnl binnen organische chemie)
- Minor BioNanotechnology

Achtergrond

- Master Moleculaire Wetenschappen RU
- PhD Bio-Organische Chemie @ RU Jan van Hest

Today

Importance of the relation between Chemistry and Biology

- Nobel Prize 2022
  - Orthogonal conjugation
  - Bio-orthogonal conjugation
  - Example of application
- Nobel Prize 2024
- Chemically manipulating proteins
- Example nanomedicine (ADCs)

- Fruitful marriage Chemistry and Biology

Nobel Prize Chemistry 2022

“ The Nobel Prize in Chemistry 2022 was awarded jointly to **Carolyn R. Bertozzi, Morten Meldal** and **K. Barry Sharpless** "for the development of click chemistry and bioorthogonal chemistry". ”

- Introduction Click chemistry
- Bio-orthogonal upgrade

Application shows intertwining Chemistry and Biology disciplines

Nobel Prize Chemistry 2022

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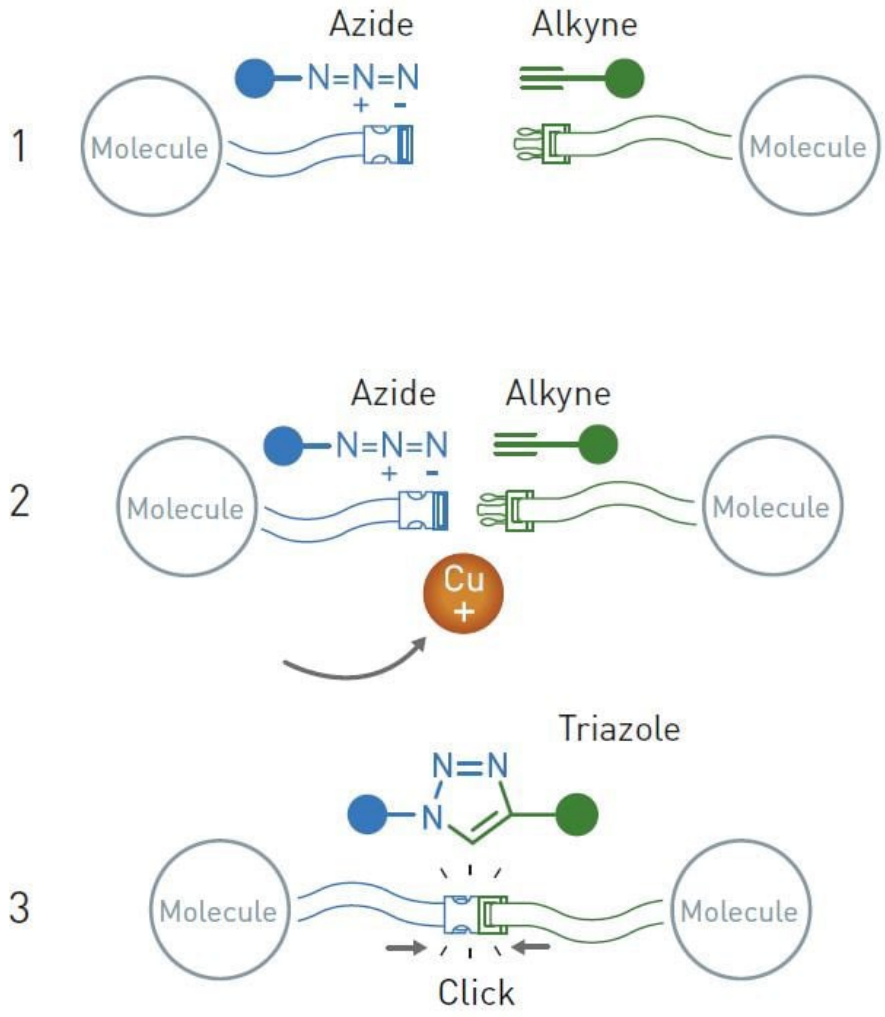
Nobel Prize Chemistry 2024 Click Chemistry



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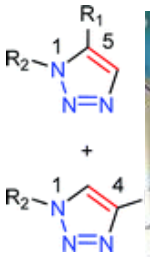
Nobel Prize Chemistry 2024 Click Chemistry; Cu(I)-catalyzed azide alkyne cycloaddition (CuAAC)

- Alkyne is dipolarophile
- Azide 1,3 dipolar compound stable against:
  - H_2O
  - O_2
  - Many organic synthesis conditions



- Copper as catalyst
  - regioselectivity → 1,4-disubstituted 1,2,3-triazoles
  - Often Cu(II)-salt with reducing agent is used
    - more stable
    - more pure
    - more effective
    - Cheaper

- Product is the heterocycle: triazole
- Working with azides → explosion danger

http://www.organic-chemistry.org/namedreactions/huisgen-1,3-dipolar-cycloaddition.shtm

https://i0.wp.com/cenblog.org/the-safety-zone/files/2014/06/UMN-accident-hood-pic-by-Erik-Goebel.jpg?resize=300%2C225

CuAAC is a Orthogonal conjugation

*Reactions are orthogonal if **in a reaction tube** they react fast and reactants **react only with each other**.*

Criteria of orthogonality:

- *no interference or cross-reactivity with other in test-tube occurring functional groups*
- *very reactive towards each other*
- *very fast reaction*
- *high conversion*

Nobel Prize Chemistry 2024 Click Chemistry; Cu(I)-catalyzed azide alkyne cycloaddition (CuAAC)

Working in living systems;

- Azide is very stable +
- Azide is non reactive towards other compounds (within a living system) +
- Alkyne is not very reactive +
- Reaction needs copper as catalyst – (BIG MINUS)

- So need for bio-orthogonal click reaction

http://www.organic-chemistry.org/namedreactions/huisgen-1,3-dipolar-cycloaddition.shtm

Bioorthogonal conjugation

similar to orthogonal but additionally:

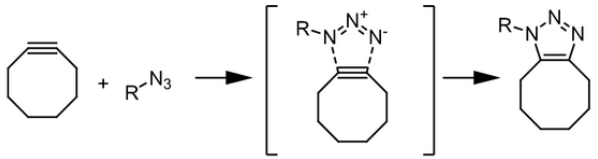
1. *no interference or cross-reactivity with naturally occurring functionalities*
2. *reactivity under mild, physiological conditions*
3. *lack toxicity*
4. *minimal perturbation of biological functionality of biomolecule*

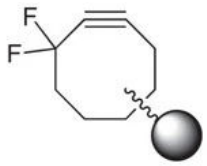
- Thus in comparison to orthogonal reaction:
  - Much more specific
  - Reactions can be performed in a biological system (protein, cells, body)
    - thus including this variaty of other reactive species!

criteria are rewritten from: A. Borrmann, Expanding and exploring the bioconjugation toolbox. 2016

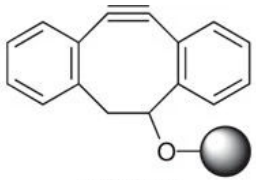
Nobel Prize Chemistry 2024 Click Chemistry; Strain Promoted Azide Alkyne cyclo addition (SPAAC)

- Reaction of azide with strained alkyne
  - strained cyclic alkyne
  - spontaneously
  - fast

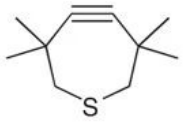




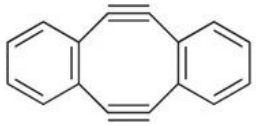
DIFO (1)



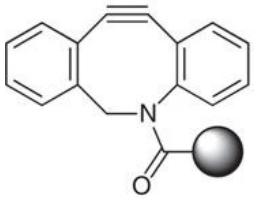
DIBO (2)



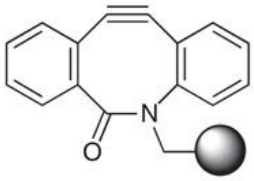
TMTH (5)



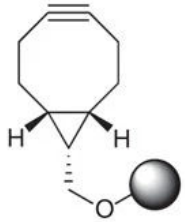
Sondheimer diyne (7)



DIBAC/DBCO (3)



BARAC (4)



BCN (6)

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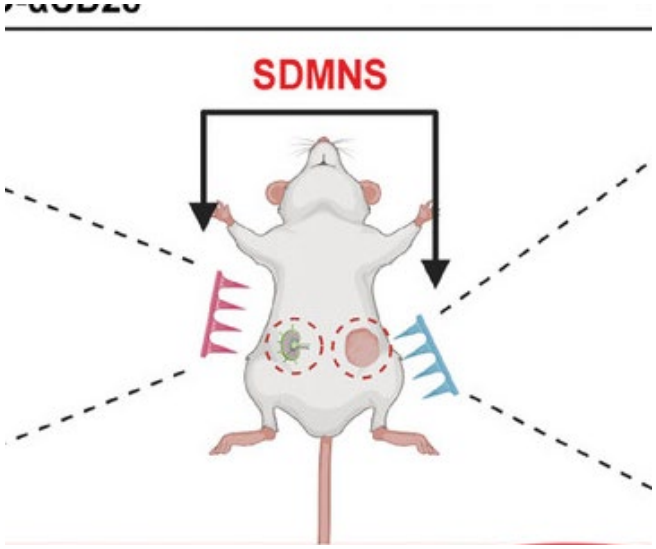
Recent example click chemistry in living system (SPAAC)

Anti cancer treatment

- Low impact immunotherapy
  - Microneedles (spatially distributes microneedle system)
  - Click chemistry within the living system



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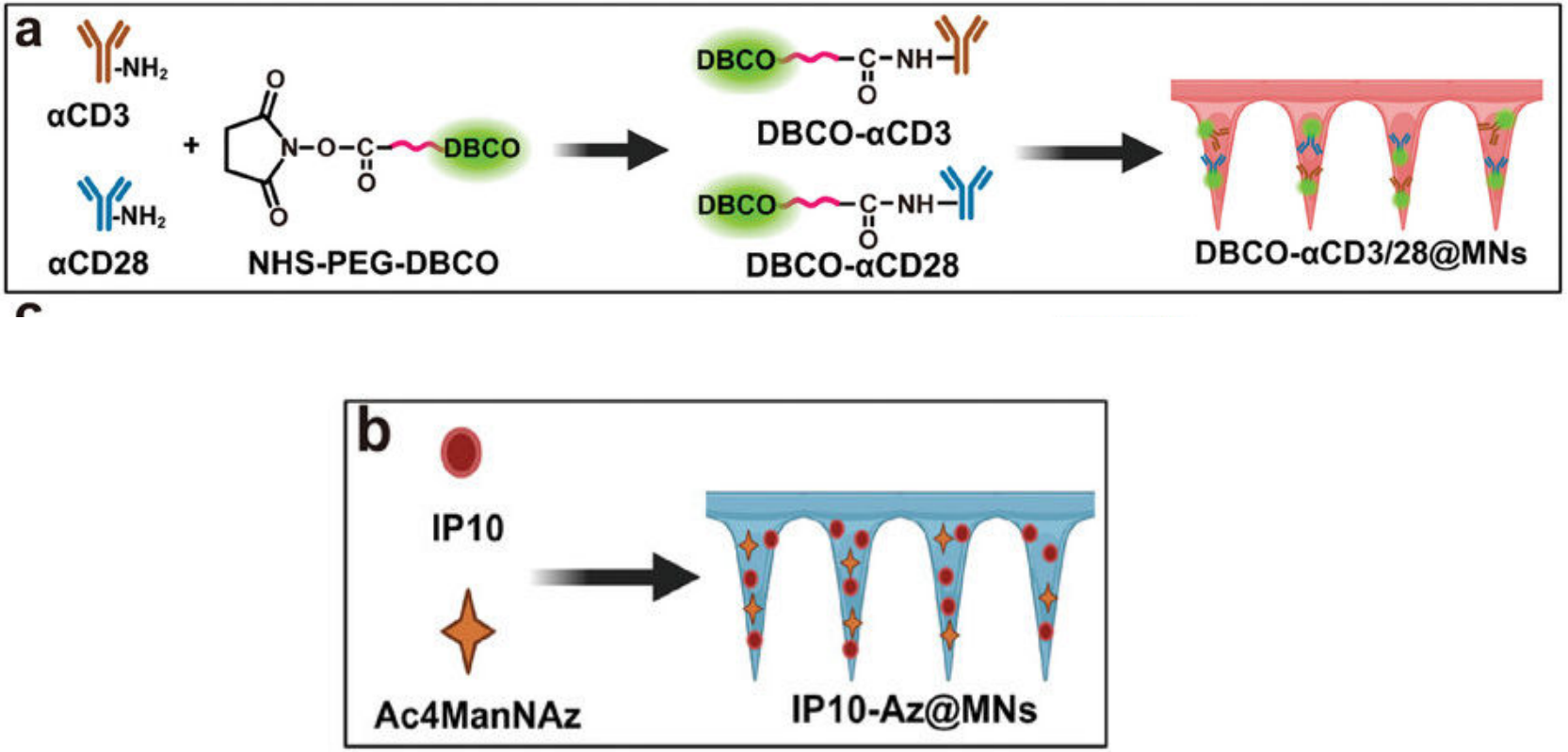
Recent example click chemistry in living system (SPAAC)



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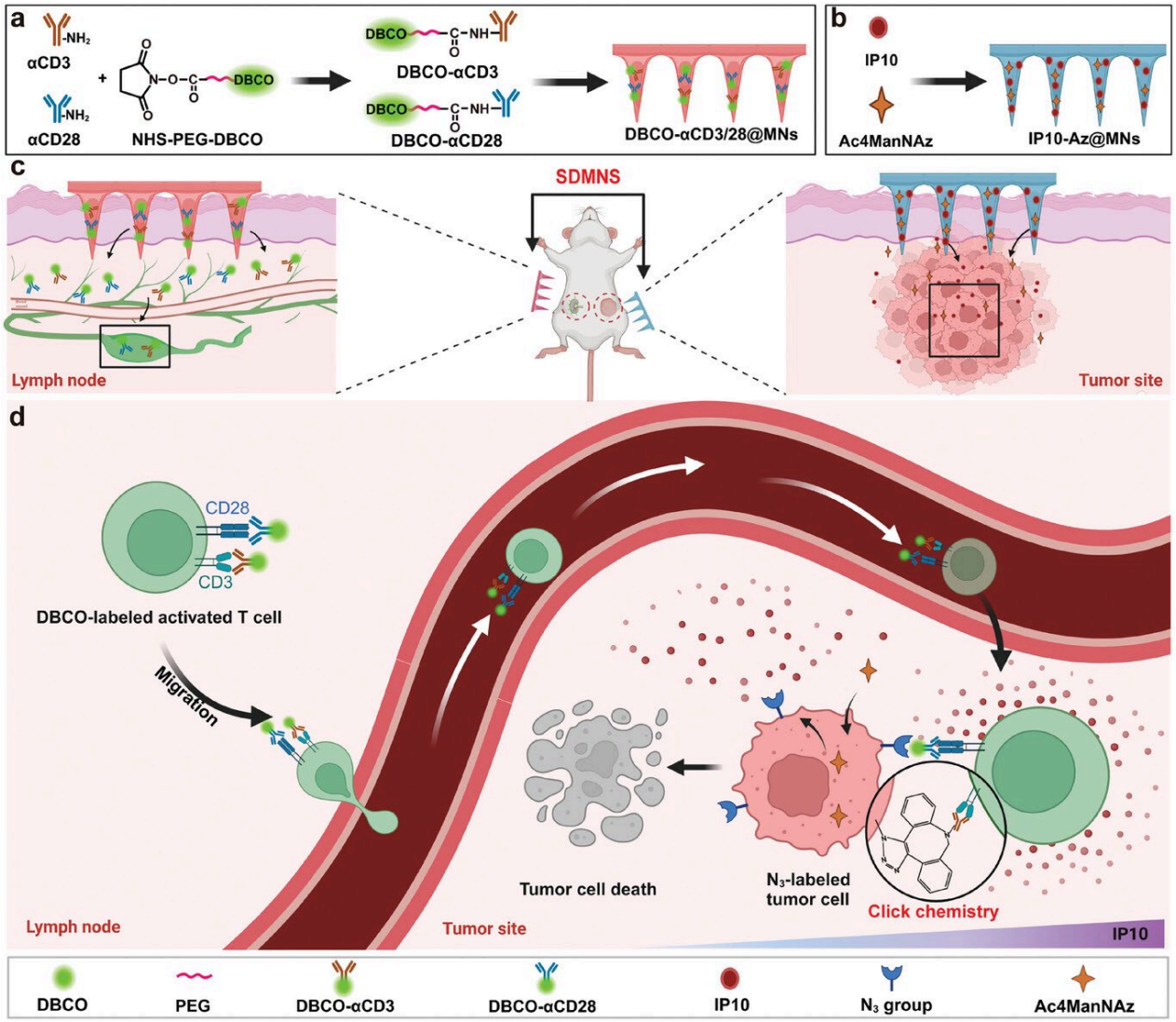
Recent example click chemistry in living system (SPAAC)



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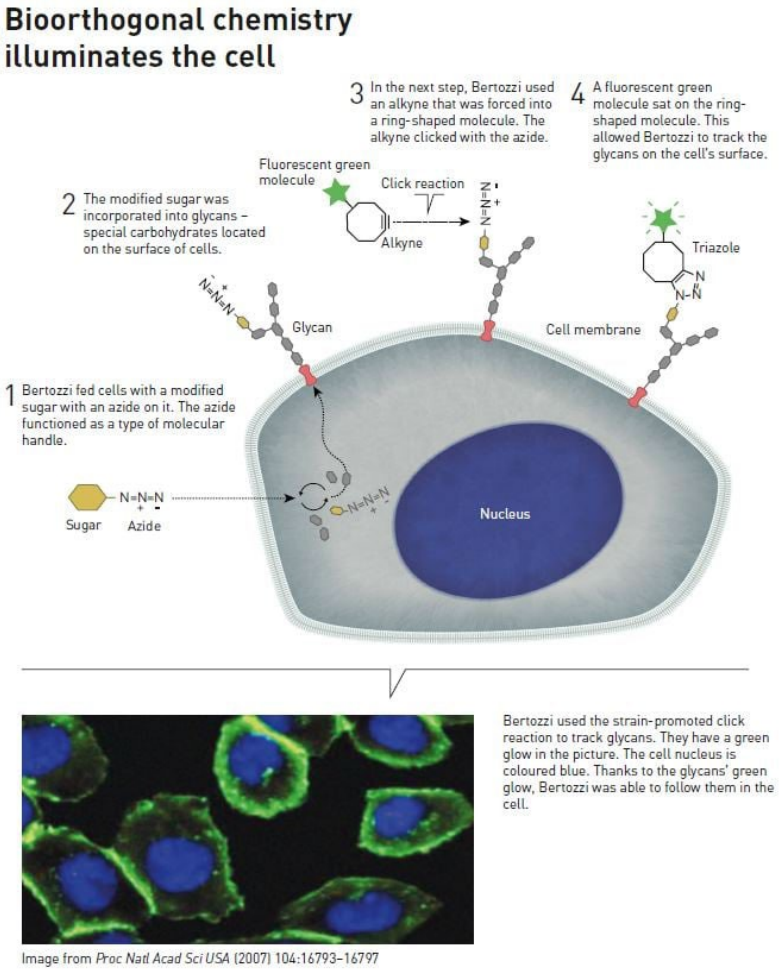
Another example Nobel Prize Chemistry 2022



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Nobel Prize Chemistry 2022 onwards

- This click chemistry forms the starting point for many

bioconjugation methods

Where two molecules are linked together of which ate least one is a biomolecule

Nobel Prize Chemistry 2022

Shows intertwining Chemistry and Biology disciplines

- Nature as holy grail of chemical complexity
- Development of Click Chemistry (Green Chemistry)
- Bio-orthogonal Chemistry
- Manipulating with(in) living organisms

Nobel Prize Chemistry 2024

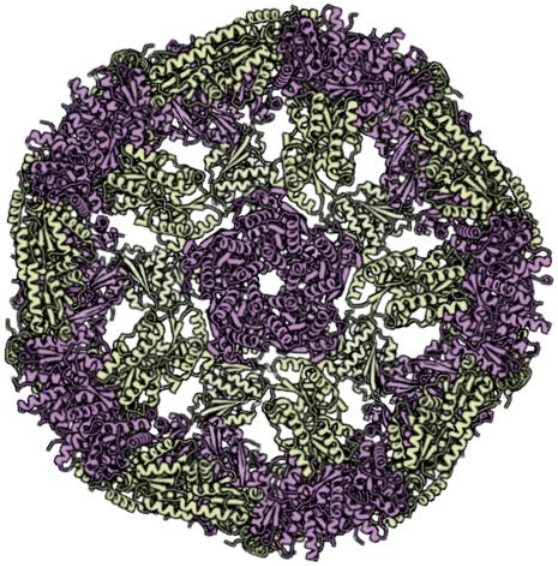
“ **Demis Hassabis** and **John M. Jumper** have successfully utilised artificial intelligence to predict the structure of almost all known proteins. **David Baker** has learned how to master life’s building blocks and create entirely new proteins. ”

- Shows intertwining Chemistry and Biology disciplines
- Signals importance of Proteins within the field of Chemistry and Physics
  - Their structure
  - Their function
  - How these correlate and can be MANIPULATED

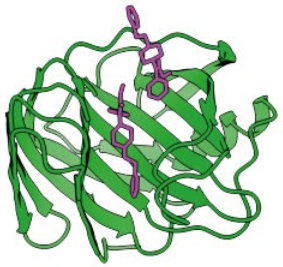
Nobel Prize Chemistry 2024

Nobel Prize Chemistry 2024

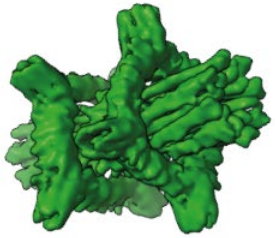
Baker's computationally designed proteins



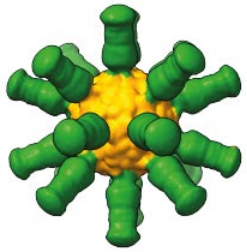
2016: New nanomaterials where up to 120 proteins spontaneously link together.



2017: Proteins that bind to an opioid called fentanyl (purple). These could be used to detect fentanyl in the environment.



2022: Proteins that function as a type of molecular rotor.



2021: Nanoparticles (yellow) with proteins imitating influenza virus on the surface (green) that can be used as a vaccine for influenza. Successful in animal models.

2024: Geometrically shaped proteins that can change their shape due to external influences. Could be used for producing tiny sensors.

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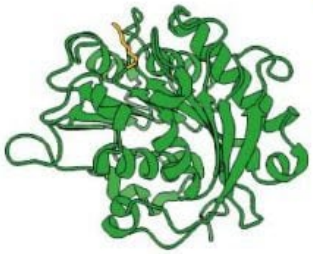
Downloaded 23-09-2025 from: https://www.nobelprize.org/uploads/2024/10/fig4_ke_en_24_2.pdf

Nobel Prize Chemistry 2024

Predictions of protein structures AlphaFold2 (Hassabis and Jumper)

2022: Part of a huge molecular structure in the human body. More than a thousand proteins form a pore through the membrane surrounding the cell nucleus.

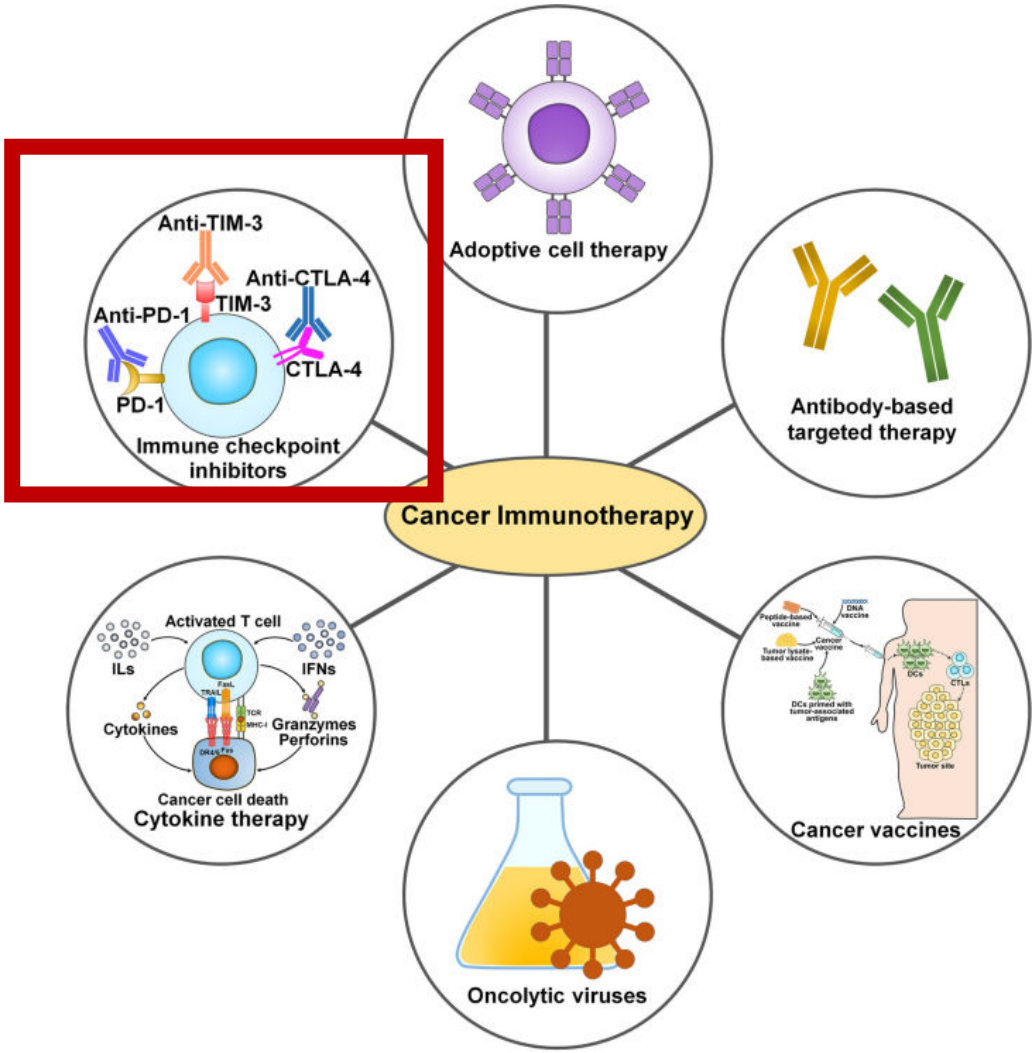


2022: Natural enzymes that can decompose plastic. The aim is to design proteins that can be used to recycle plastic.

2023: A bacterial enzyme that causes antibiotic resistance. The structure is important for discovering ways of preventing antibiotic resistance.

Downloaded 23-09-2025 from: https://www.nobelprize.org/uploads/2024/10/popular-chemistryprize2024-figure5-1024x493.jpg

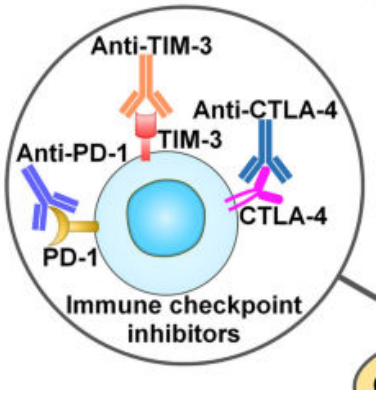
Examples of chemically manipulating proteins/use proteins



Downloaded from: https://molecular-cancer.biomedcentral.com/articles/10.1186/s12943-024-02214-5

Examples of chemically manipulating proteins/use proteins

Immune checkpoint inhibitor example; PD-1



- Cell surface receptor on T-cells (& B-cells)
- Downregulating the immune response
  - Suppressing T-cell inflammatory activity
  - Important for prevention autoimmune diseases
- T-cells exhibit anti-PD-1 on their surface
- Bonding anti-PD-1 and PD-1 (on cancer cell) → prevents T cell attack

Many different immune checkpoint inhibitors are known

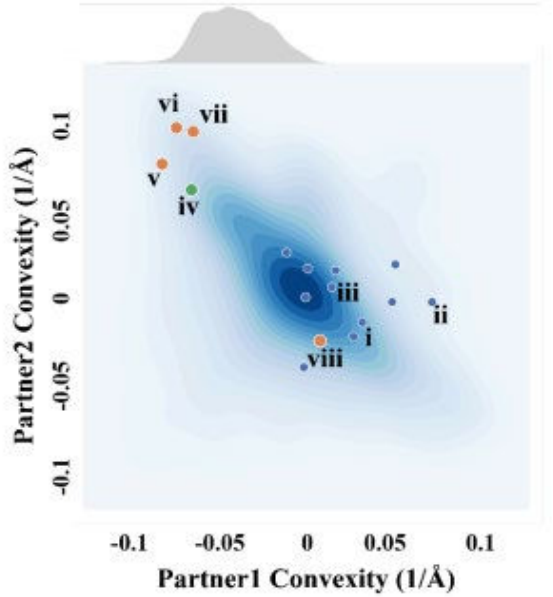
Ideally find a method to prevent the binding of T-cells to these immune checkpoint inhibitors

Downloaded from: https://molecular-cancer.biomedcentral.com/articles/10.1186/s12943-024-02214-5

Examples of chemically manipulating proteins/use proteins

Baker's group example

- Designing high affinity binder to immune checkpoint inhibitors
- Several Immune checkpoint inhibiters show at interaction site high curvature (rounding)
- Hard to design proteins with this type of curvature.



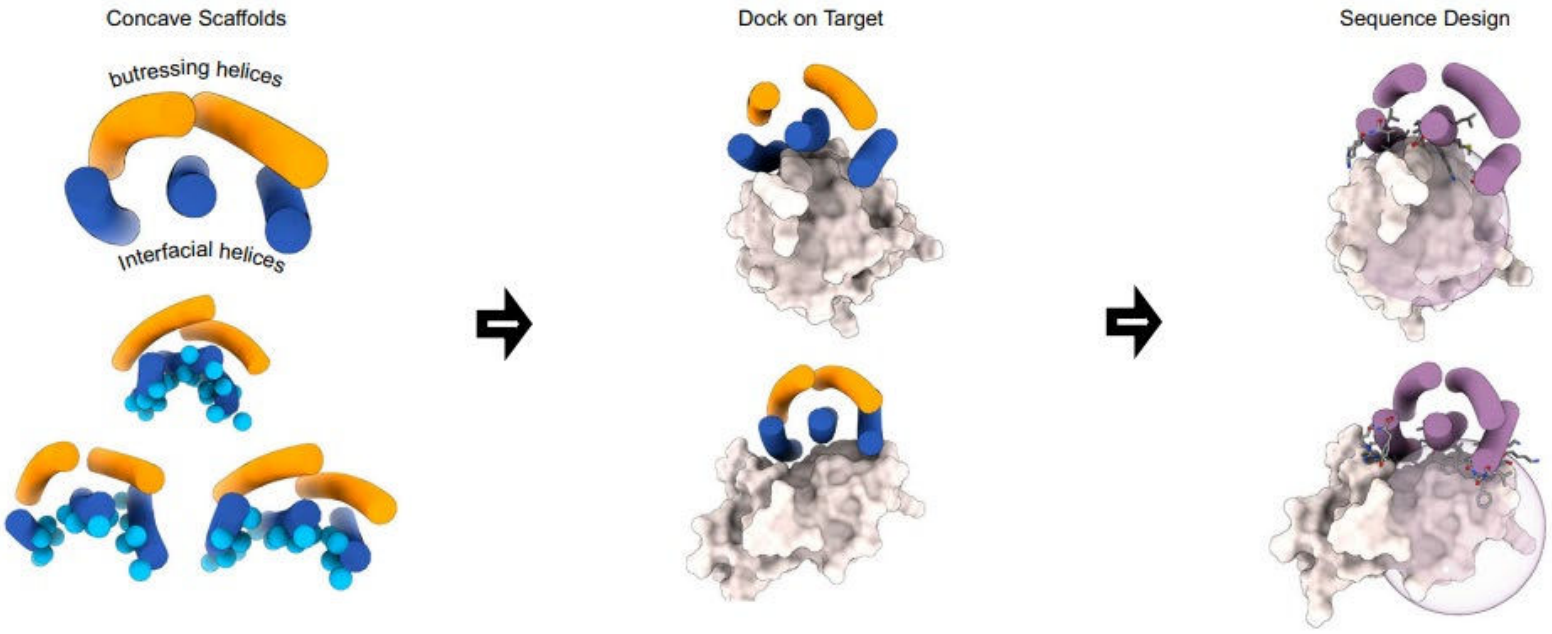
- Partner 1: designed partners
- Partner 2: target
- Blue dots designed up to now
- Orange dots several known native protein complexes
- Green dot: New design

From: Yang, W., Hicks, D.R., Ghosh, A. *et al.* Design of high-affinity binders to immune modulating receptors for cancer immunotherapy. *Nat Commun* **16**, 2001 (2025). https://doi.org/10.1038/s41467-025-57192-z

Examples of chemically manipulating proteins/use proteins

Baker's group example

- Helical concave scaffolds were tailored to convex target sites (like several Immune checkpoint inhibitors)



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Perfect fit

Both these Nobel prize winners combine Chemistry and Biology to come to a perfect fit

- ***Drug discovery***
- ***Green Chemistry***
- ***Material sciences***
- ***Many more…***

Perfect Marriage

Importance to gain knowledge interdisciplinary
Learn from and with each other
No knowledge, no discussion

Questions?