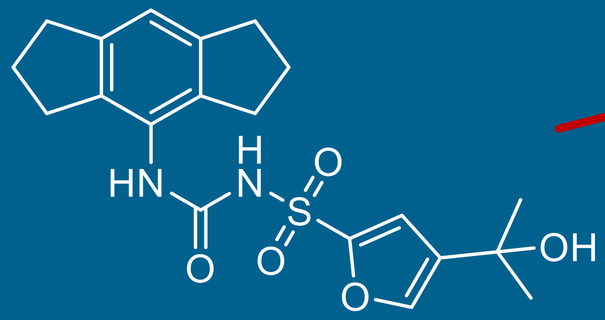
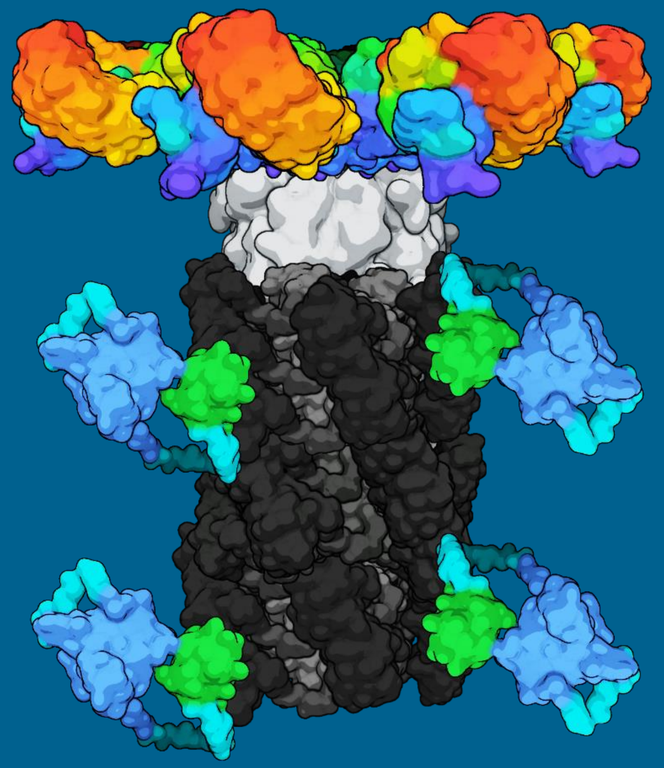
GOETHE UNIVERSITÄT FRANKFURT AM MAIN

Entwicklung kleinmoleküliger Inhibitoren des NLRP3-Inflammasoms

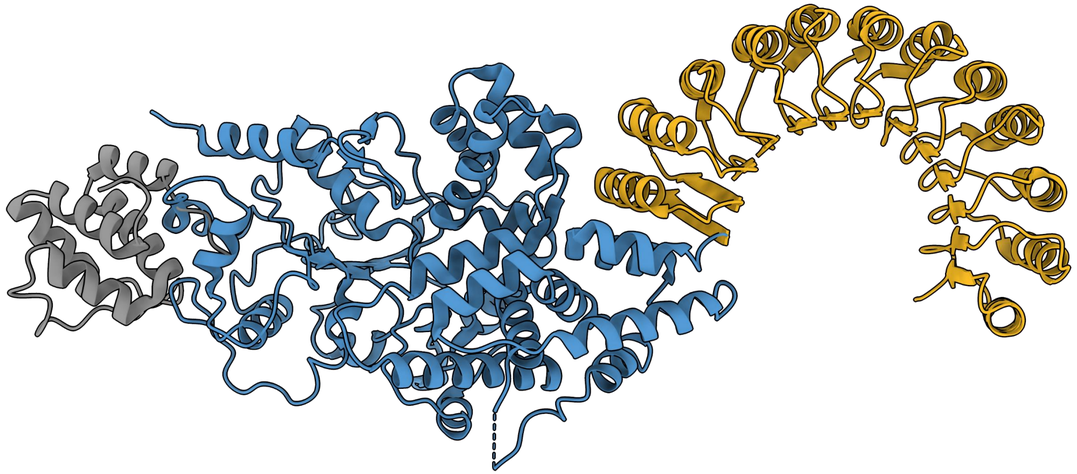


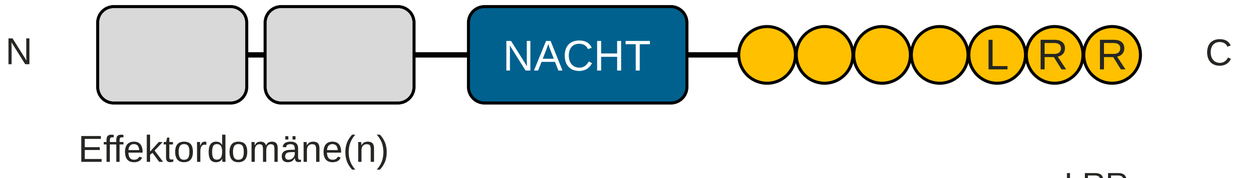


Dr. Pascal Heitel
Institut für Pharmazeutische Chemie

NOD-ähnliche Rezeptoren (NLRs)

- Nukleotidbinde- und Oligomerisierungsdomäne (NOD)-ähnliche (engl. like) Rezeptoren
- Gehört zur Familie der Musterkennungsrezeptoren
- 22 intrazelluläre Proteine (Mensch)
- Lokalisiert im Zytoplasma
- Schlüsselrole bei angeborener Immunantwort und Entzündung
- Konservierte Struktur:



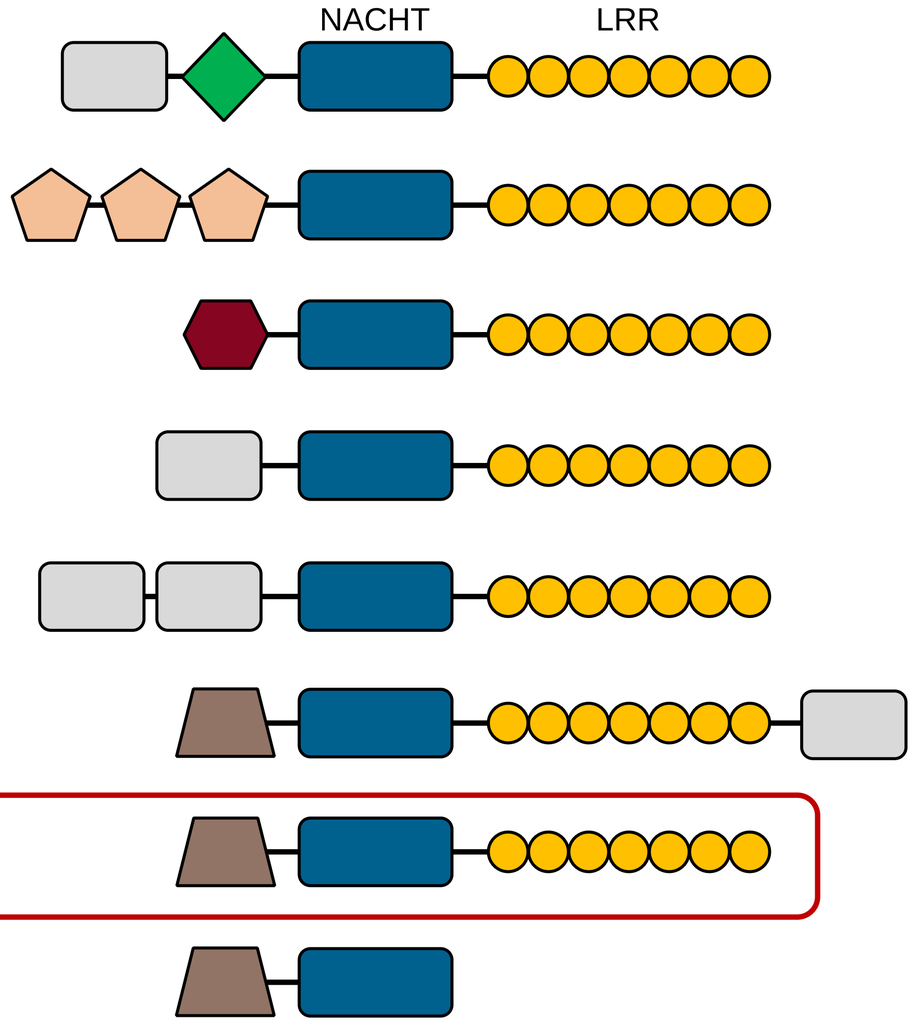


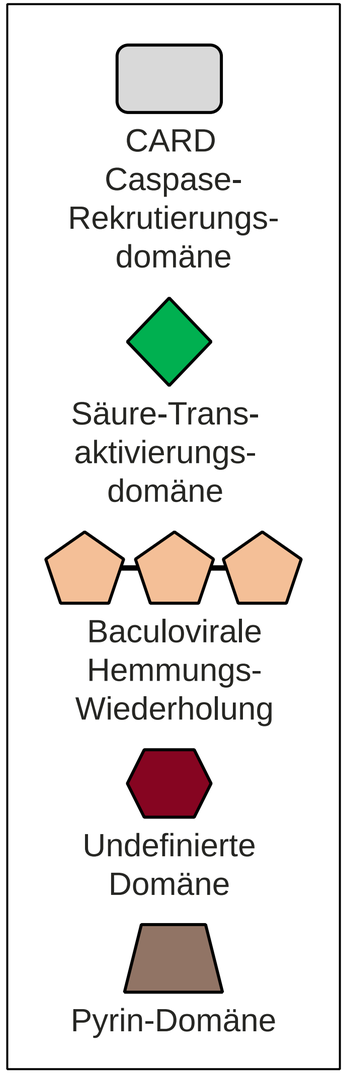
LRR	leucrinreiche Wiederholung
NACHT	Domäne in NAIP, CIITA, HET-E and TP1

Geddes, H. *et al. Nature Reviews Drug Discovery* **2009**, *8*, 465–479.

NLR Unterfamilien

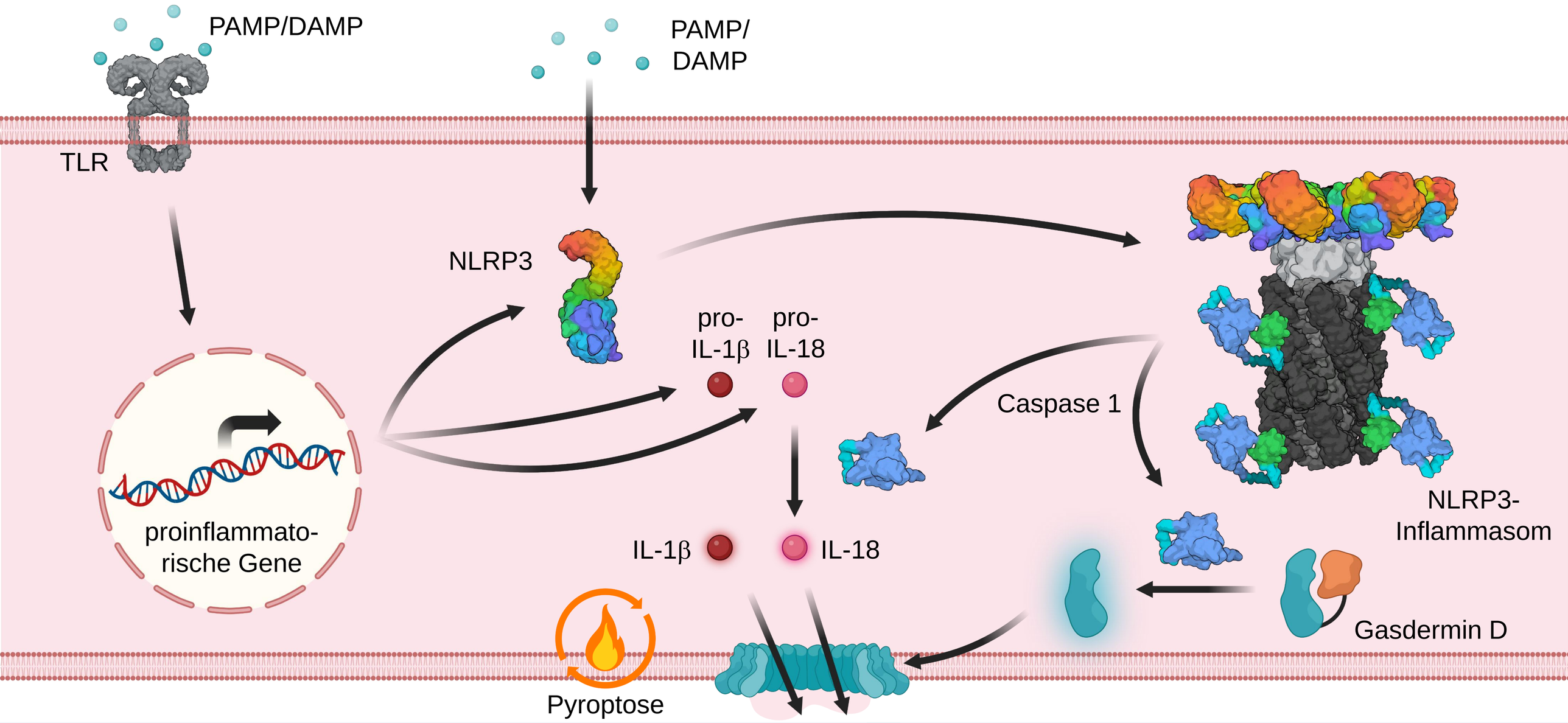
Unterfamilie	Name	Struktur
▪ NLRA	CIITA	
▪ NLRB	NAIP	
▪ NLRC	NLRC3, NLRC5, NLRX1	
	NLRC4, NOD1	
	NOD2	
▪ NLRP	NLRP1	
	NLRP2-9, NLRP11-4	
	NLRP10	





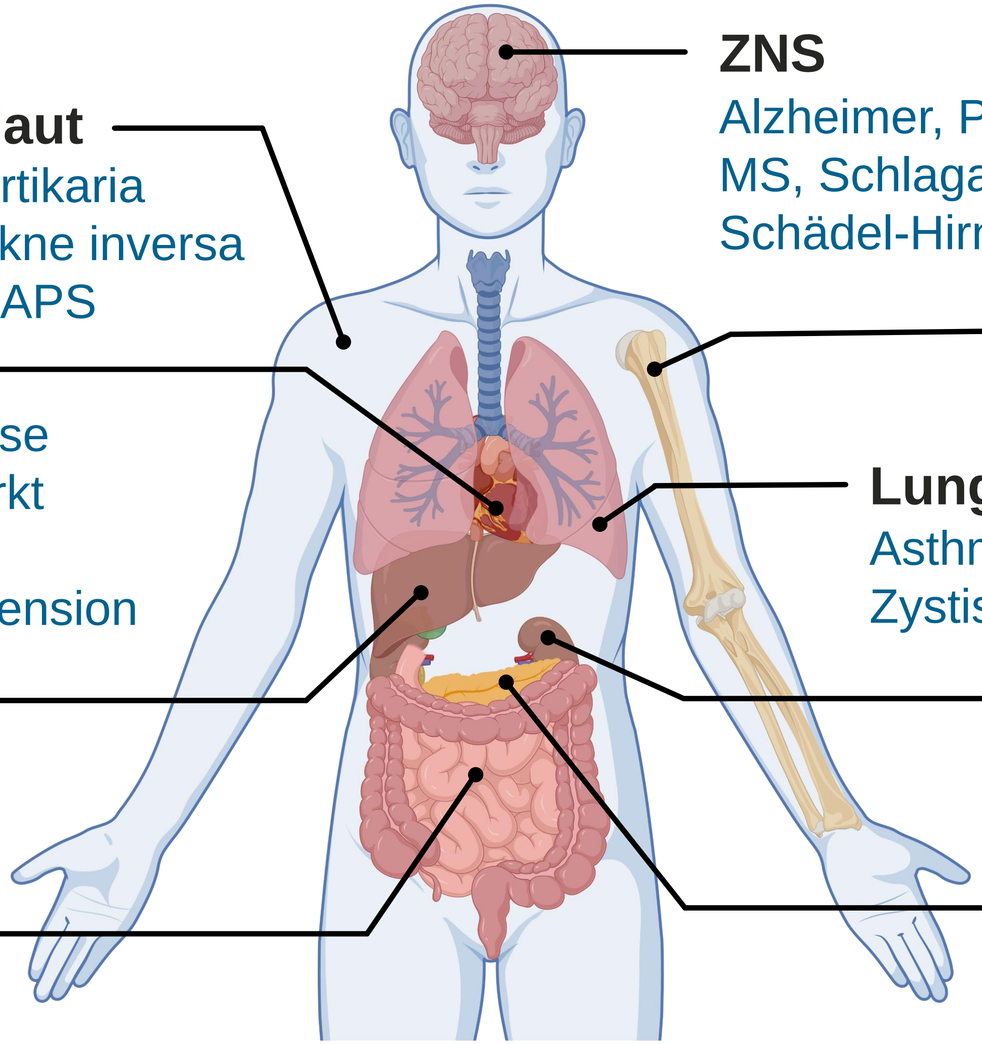
Geddes, H. *et al. Nature Reviews Drug Discovery* **2009**, *8*, 465–479.

NLRP3 Wirkmechanismus



Fu, Wu *Annu. Rev. Immunol.* **2023**, *41*, 301–16.

NLRP3 – Therapeutisches Potenzial



ZNS
Alzheimer, Parkinson,
MS, Schlaganfall,
Schädel-Hirn-Trauma, CAPS

Haut
Urtikaria
Akne inversa
CAPS

Knochen
Rheumatoide Arthritis
Gicht, CAPS

Herz
Atherosklerose
Myokardinfarkt
Perikarditis
KHK, Hypertension

Lunge
Asthma
Zystische Fibrose

Leber
Hepatitis
MASH (NASH)

Niere
CKD
CAPS

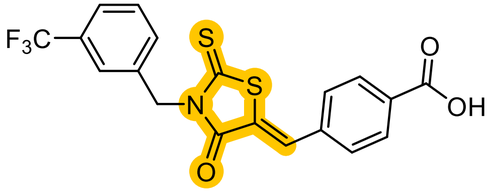
GI-Trakt
IBD

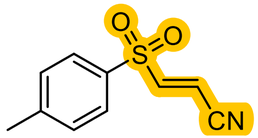
Pankreas
Pankreatitis
Diabetes

Mangaz *et al. Nat. Rev. Drug Discov.* **2018**, *17*, 588-606.

Bisher bekannte NLRP3-Inhibitoren

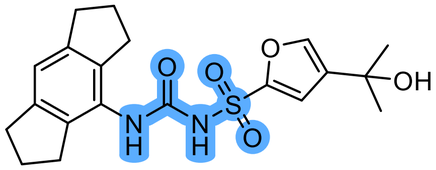
- Michael-Akzeptoren, z.B.





chemisch reaktiv
→ unselektiv

- Sulfonylharnstoffe, z.B.



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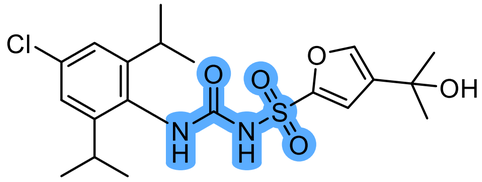
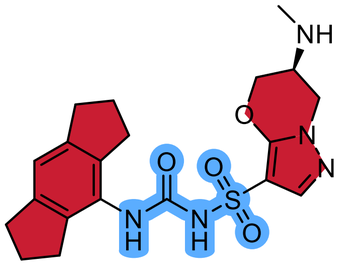
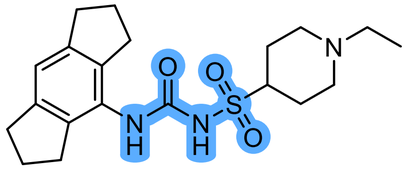
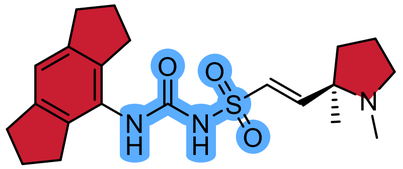








Geringe Halbwertszeit, Lebertoxizität beobachtet

Vande Walle, Lamkanfi *Nat. Rev. Drug Discov.* **2024**, *23*, 43-66. Parmar *et al. Clin. Pharm. Drug Dev.* **2023**, *12*, 202−211. Tang *et al. Clin. Transl. Sci.* **2023**, *16*, 1653−1666.

Projektziele

- Entwicklung eines NLRP3-Assaysystems
- Screening zur Identifizierung neuer Chemotypen von NLRP3-Inhibitoren mit verbessertem pharmkokinetischem Profil
  - ➢ Kombinatorischer Ansatz

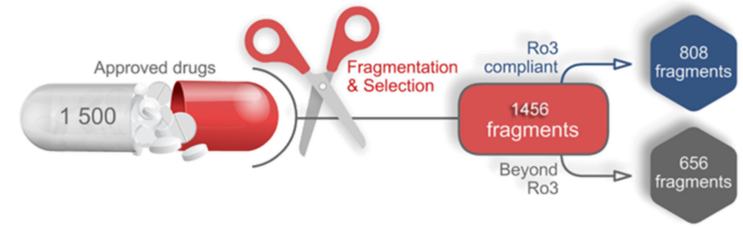
Chemical Library

1520 zugelassene Wirkstoffe

PRESTWICK CHEMICAL LIBRARIES BY GREENPHARMA

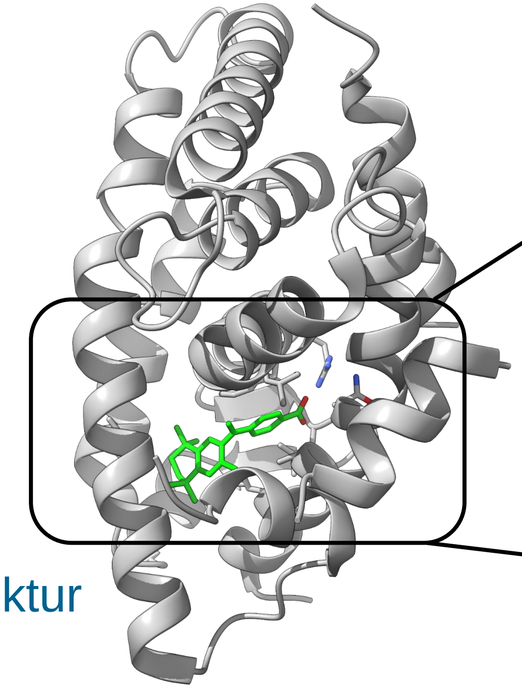
Drug-Fragment Library

1456 Wirkstofffragmente

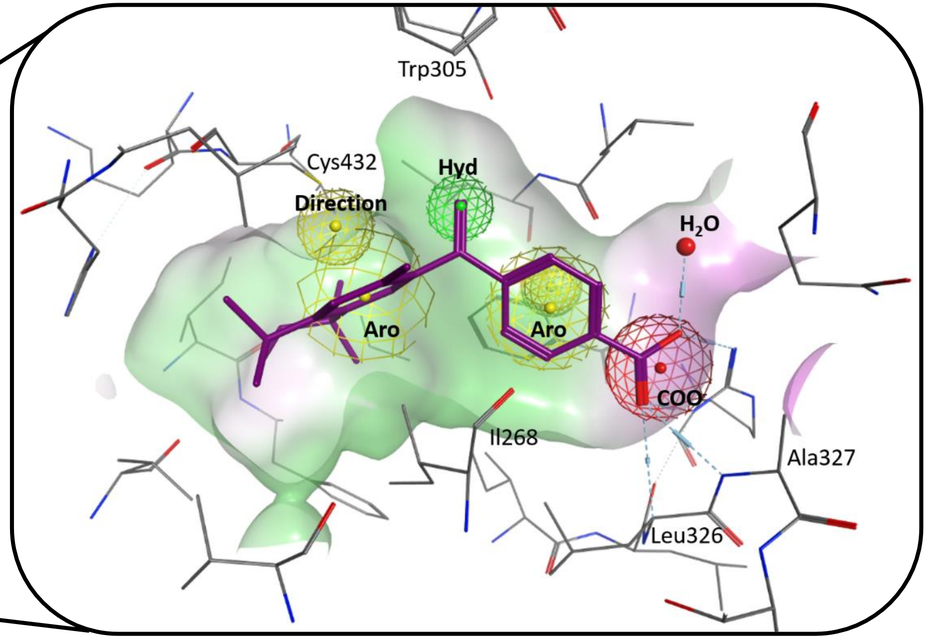


Projektziele

- Entwicklung eines NLRP3-Assaysystems
- Screening zur Identifizierung neuer Chemotypen von NLRP3-Inhibitoren mit verbessertem pharmkokinetischem Profil
  - ➢ Computerbasierter Ansatz



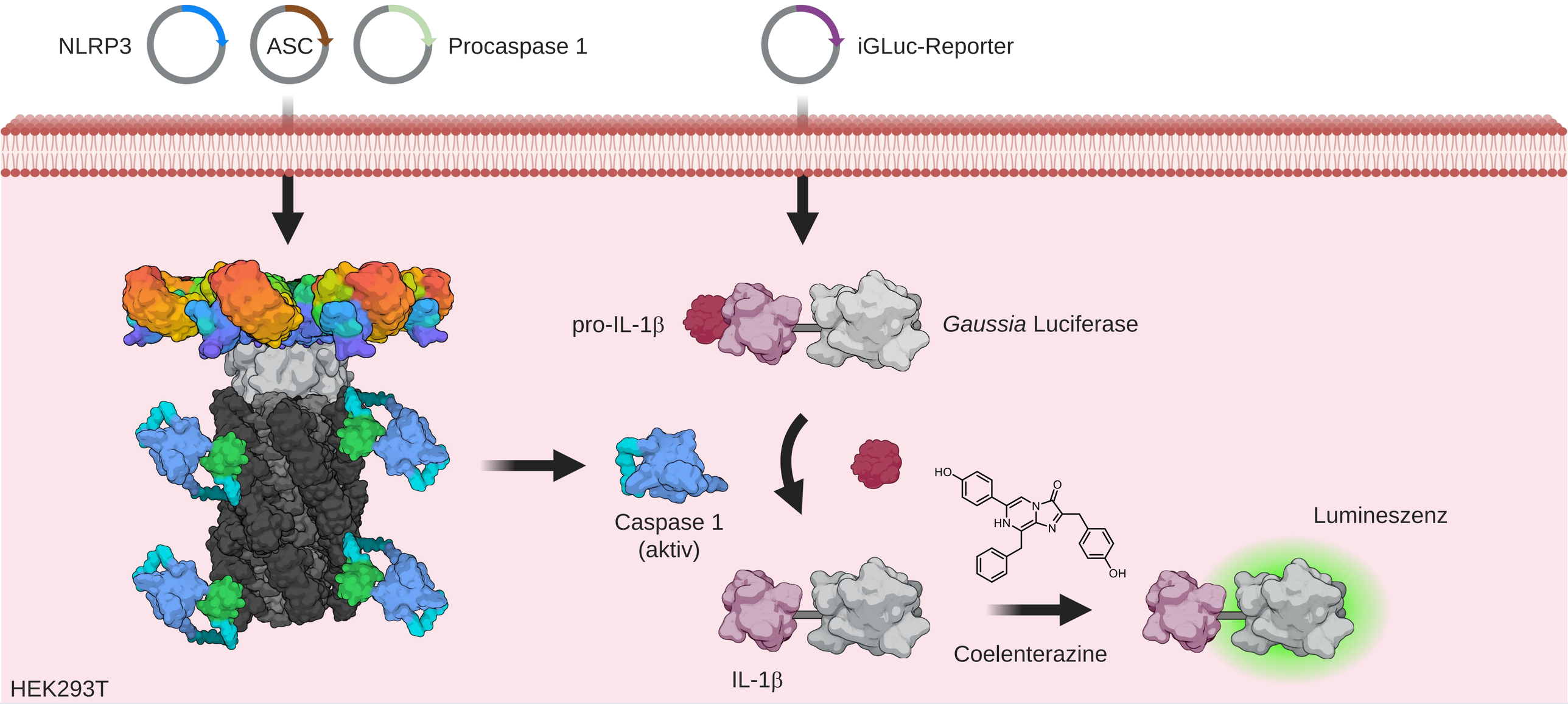
Kristallstruktur

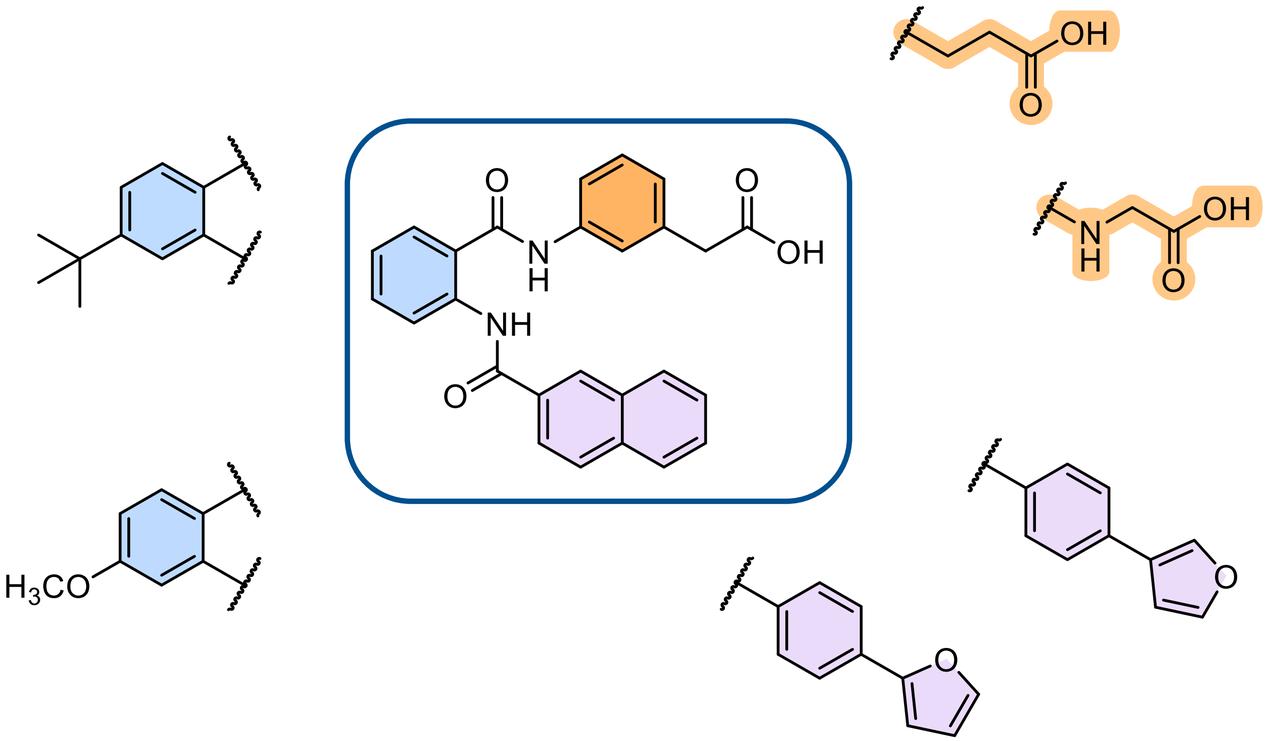


Pharmakophormodell

PDB-ID 4k6i

Das Assay-System



Ausblick

- Untersuchung der Struktur-Wirkungsbeziehung der identifizierten NLRP3-Inhibitoren
- Untersuchung der pharmakokinetischen Parameter (metabolische Stabilität, Löslichkeit, etc.)
- Präklinische Untersuchungen