



The Vollmar Lab



Dr. Karin Bartel



Dr. Simone Moser



Dr. Simone Braig



Prof. Dr.
Stefan Zahler



Dr. Karin
von Schwarzenberg

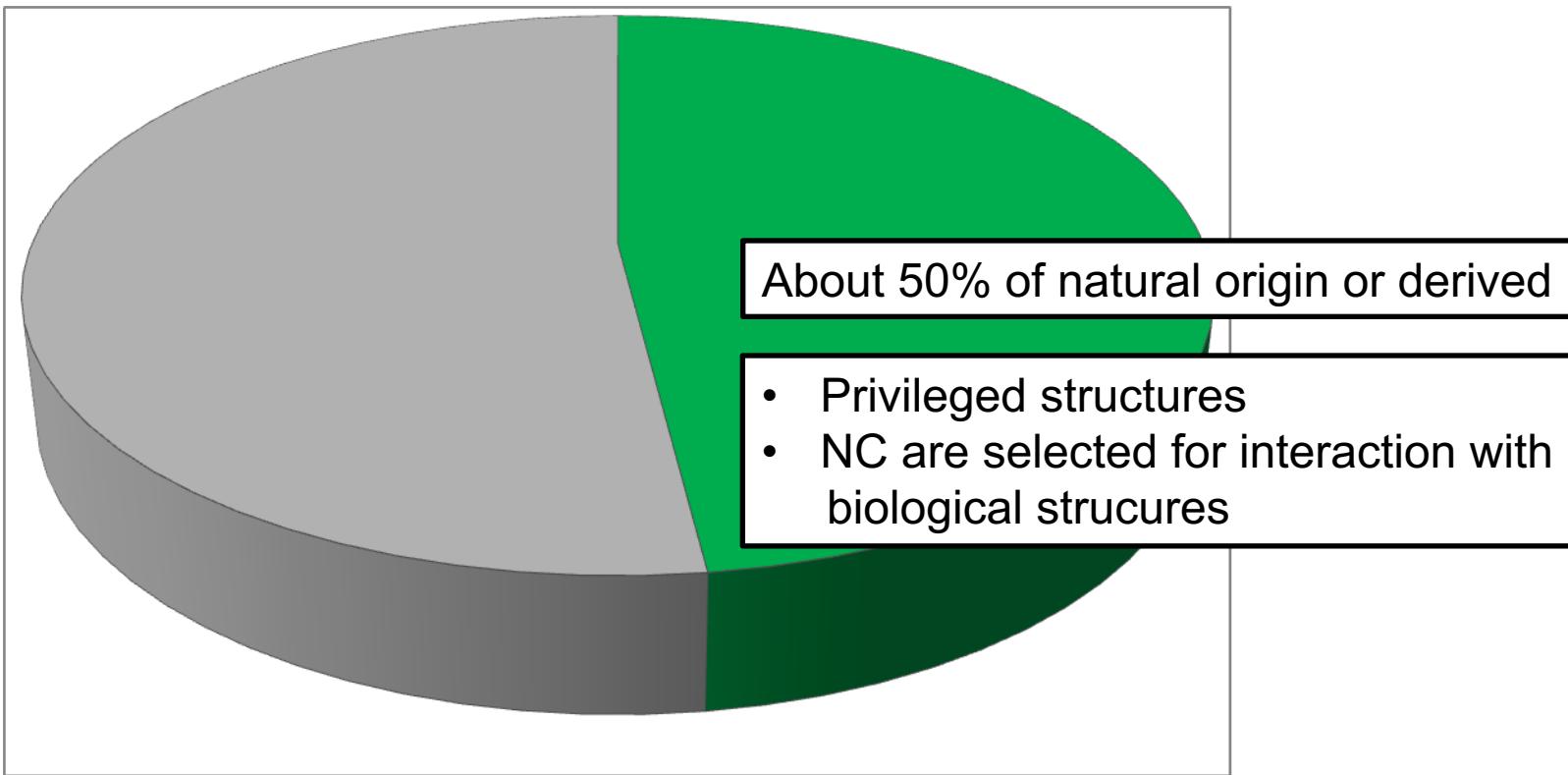
Naturstoffe
Krebsforschung



Background



Natural compounds – invaluable source for therapeutic leads

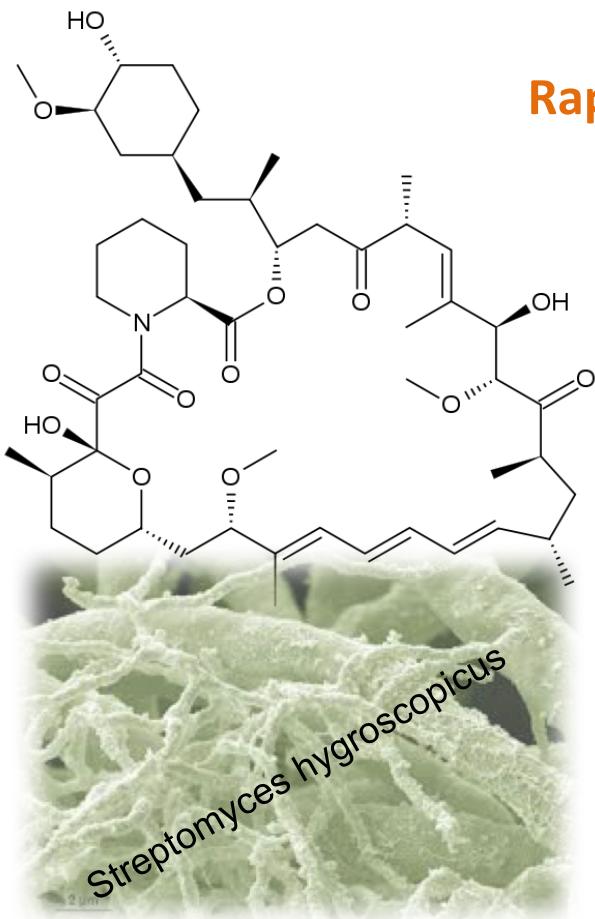


All available anticancer drugs 30 years from **1981 to 2014**

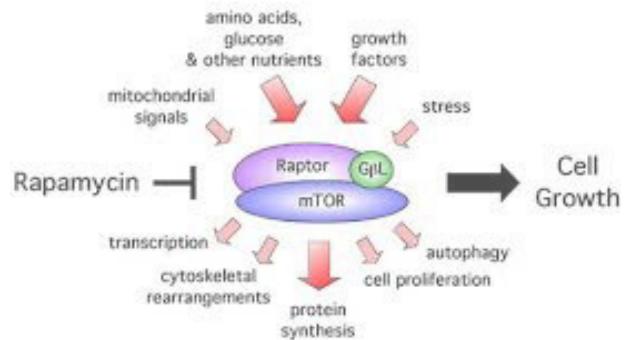
Background



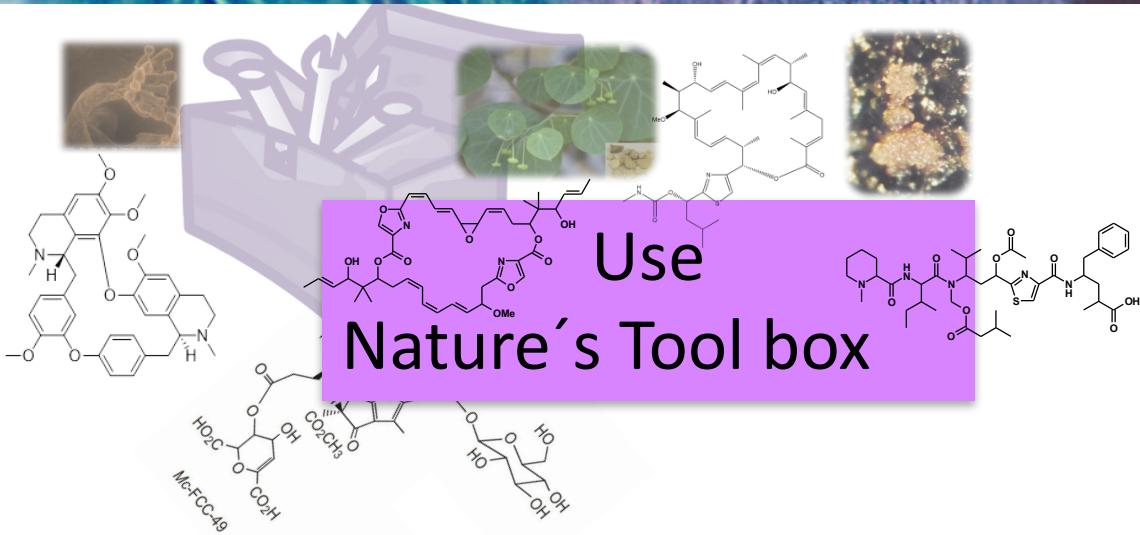
Natural compounds – indispensabile **chemical tools** to understand biological/pharmacological systems



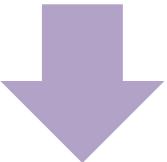
mTOR=
mammalian target of rapamycin



Our focus



- To discover innovative **anticancer** compounds
- To identify new **targets** for cancer therapy

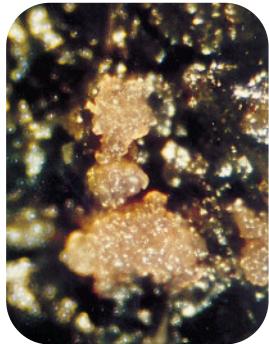
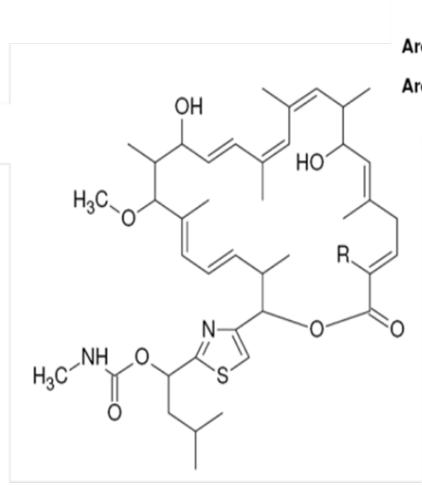


Learn more about cancer biology and cancer targets

Examples of our strategies

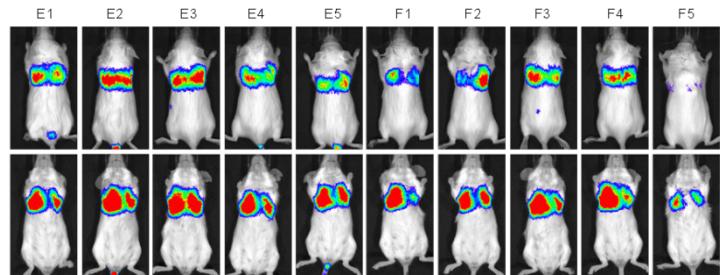


Dr. K. von
Schwarzenberg

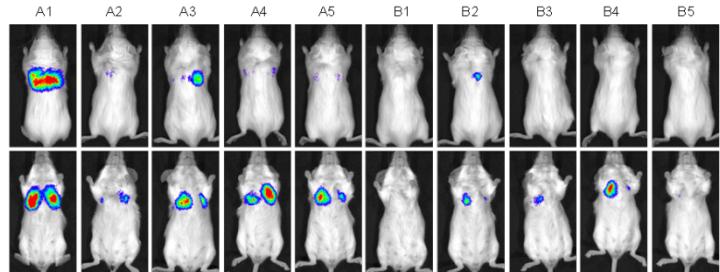


Cooperation with
Prof. Müller, HIPS

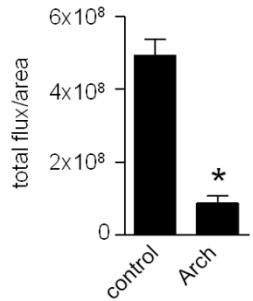
control mice



Archazolid treated mice

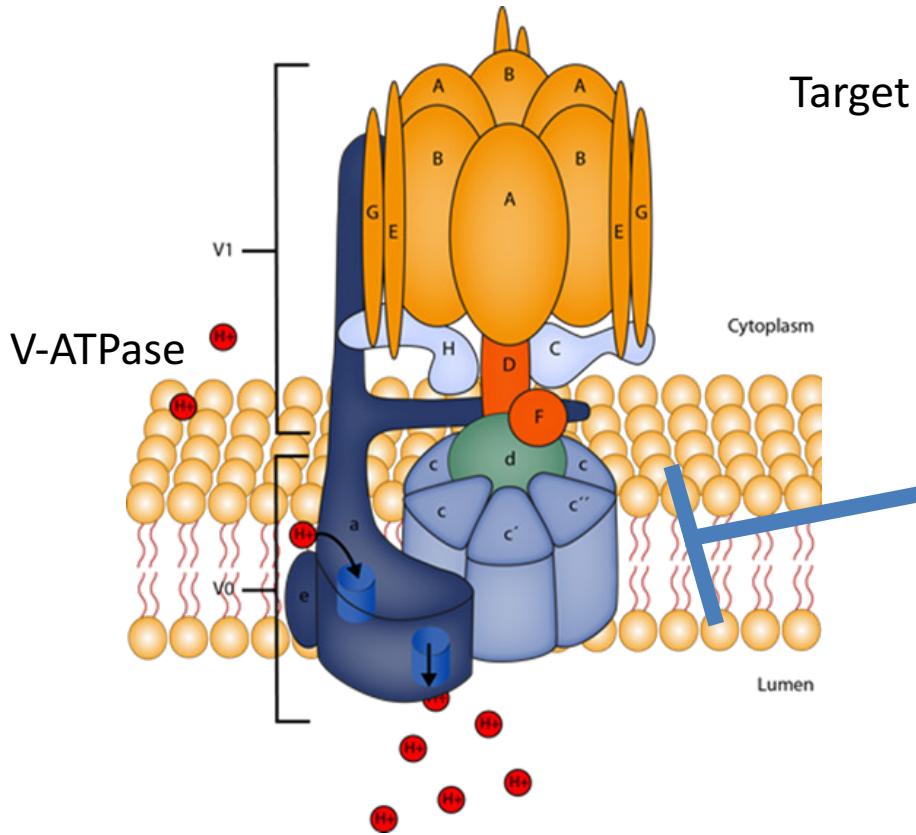


4T1-Luc mouse
mammary tumor
cells, i.v.



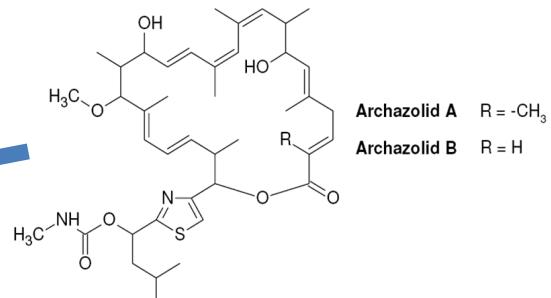
Role of target in cancer

Novel targets



Target

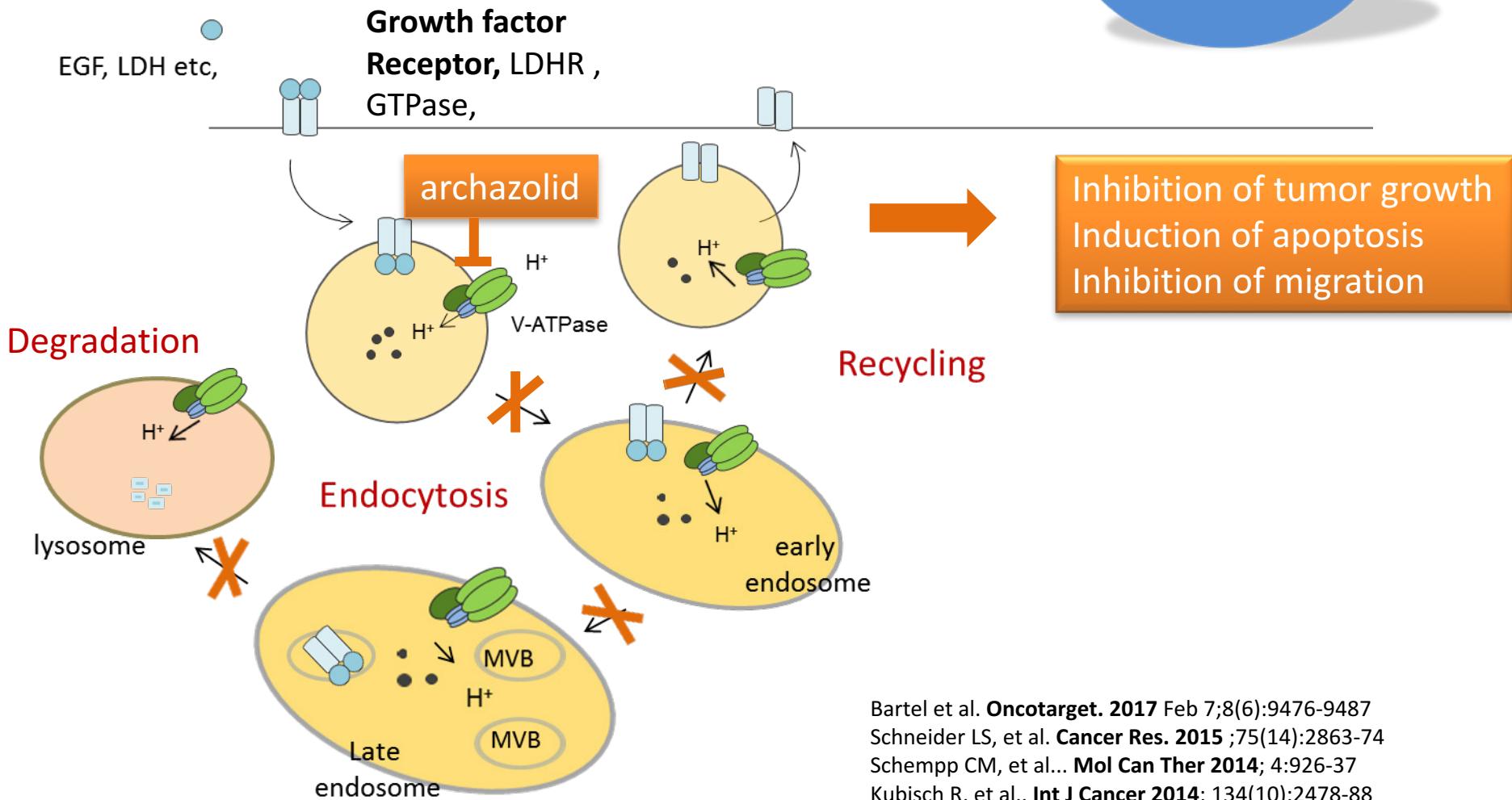
Chemical Tool



Role of V-ATPase in Cancer Growth and Metastasis ?

Mode of Action

Novel targets



Bartel et al. *Oncotarget*. 2017 Feb 7;8(6):9476-9487

Schneider LS, et al. *Cancer Res*. 2015 ;75(14):2863-74

Schempp CM, et al... *Mol Can Ther* 2014; 4:926-37

Kubisch R, et al.. *Int J Cancer* 2014; 134(10):2478-88

Von Schwarzenberg K, et al.. *Mol Oncol* 2014; 1:9-19

Rath S, et al. *Angiogenesis* 2014; 17(3):587-601

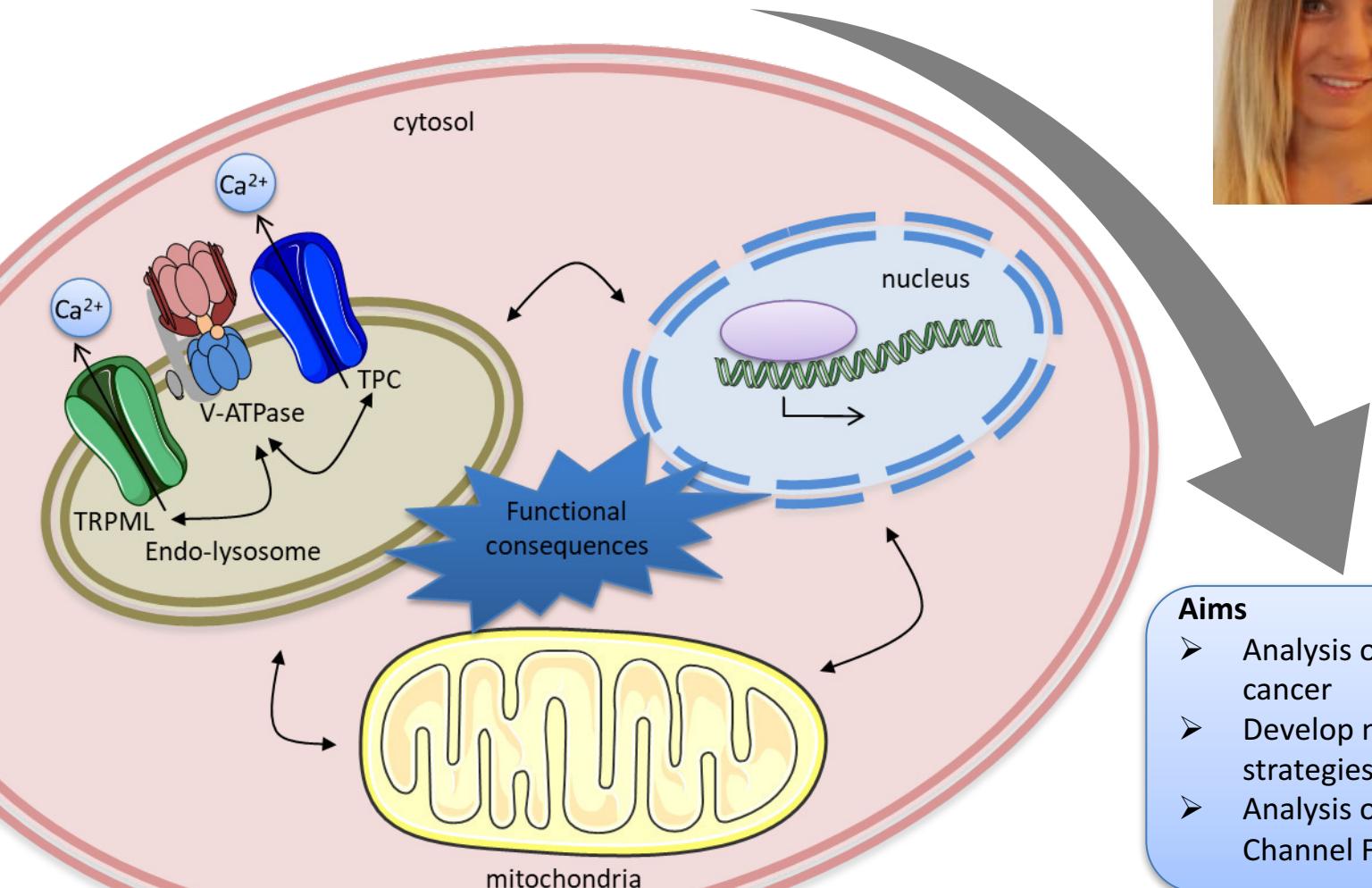
von Schwarzenberg K, et al.. *J Biol Chem*. 2013; 288(2):1385-96.

Wiedmann RM, et al.. *Cancer Res*. 2012;72(22):5976-87.

THE ENDO-LYSOSMAL SYSTEM IN THE DEVELOPMENT AND TREATMENT OF CANCER



The Endo-Lysosomal System Central regulator of cellular functions



Dr. Karin
Bartel

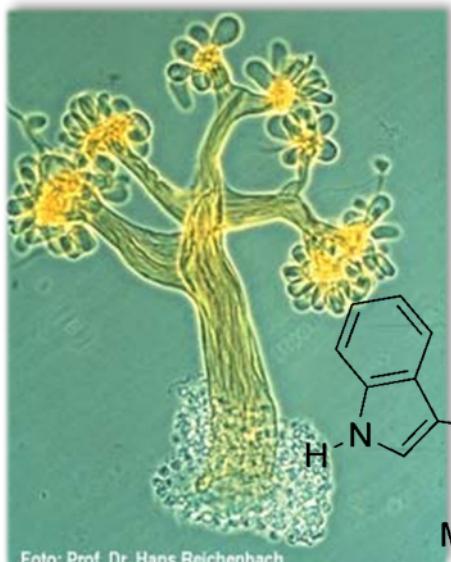


PD. Dr. Grimm

Aims

- Analysis of ES function in cancer
- Develop new therapeutic strategies
- Analysis of Endo-lysosomal Channel Function in Cancer

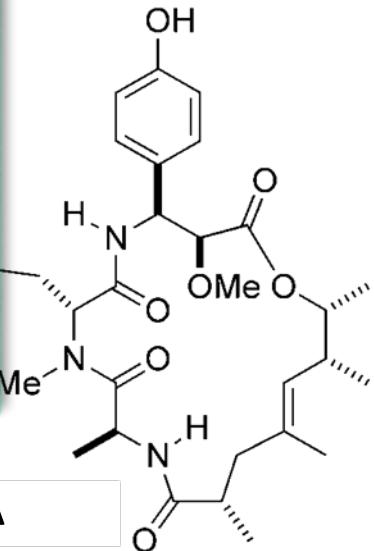
Potential of actin as tumor target



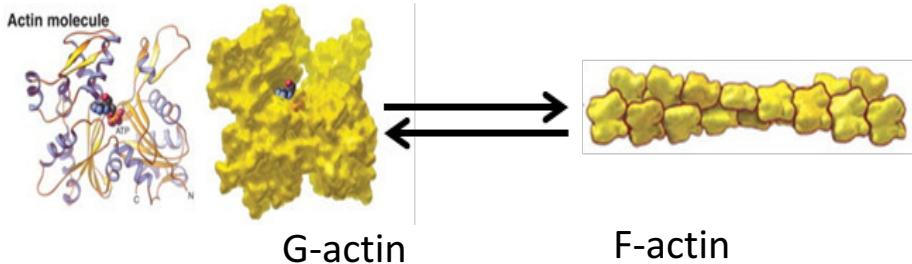
Chondramide A



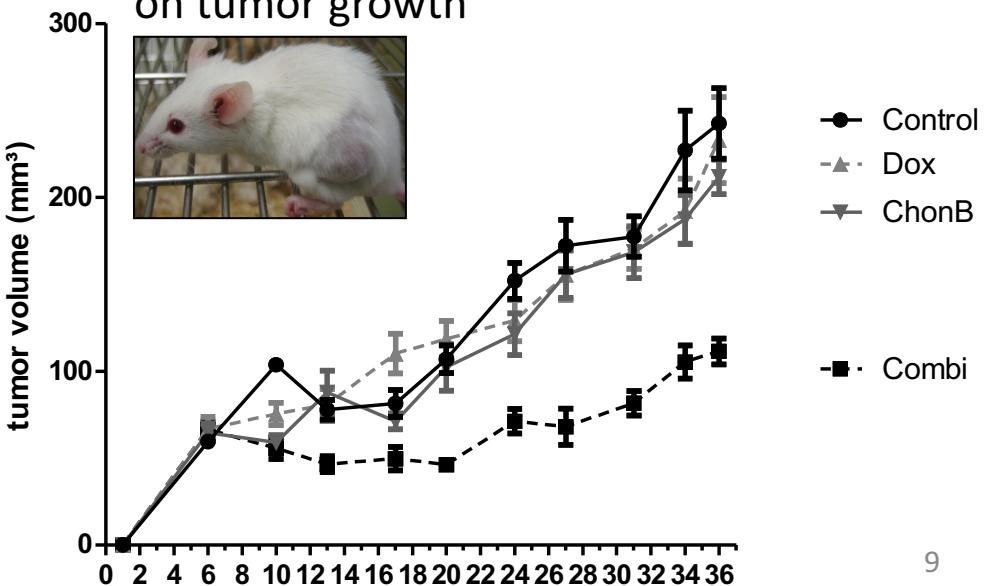
Prof. Zahler



Target:



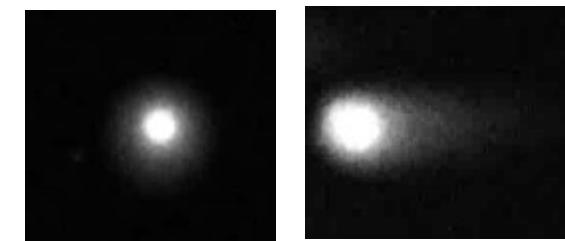
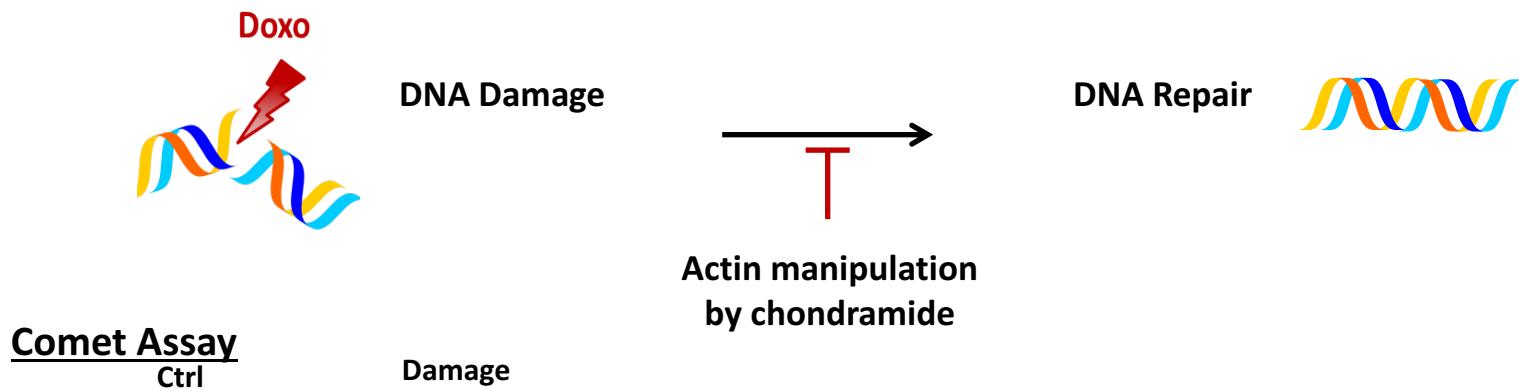
Synergistic effect with Doxorubicin on tumor growth



Role of actin in DNA damage



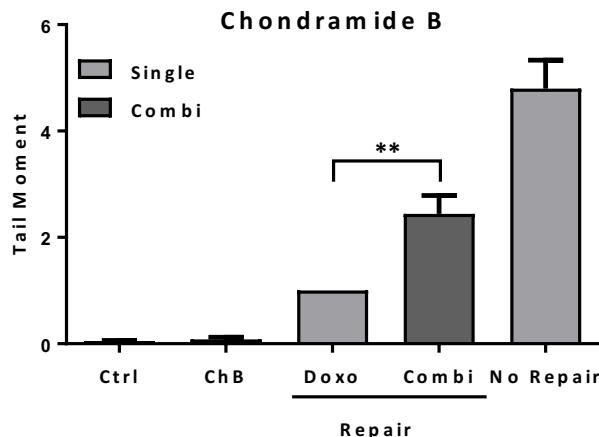
Is actin involved in DNA damage repair?



„Single Cell Electrophoresis“

→ Measures DNA strand breaks in individual cells

→ extent of damage measured by *tail moment*

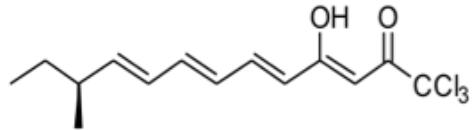


Chondramide abrogates
DNA repair mechanism

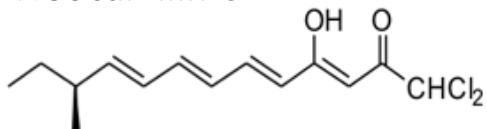
New Anticancer Compound



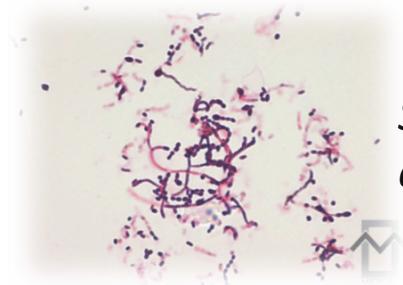
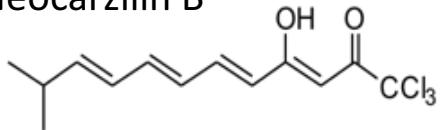
Neocarzilin A



Neocarzilin C



Neocarzilin B

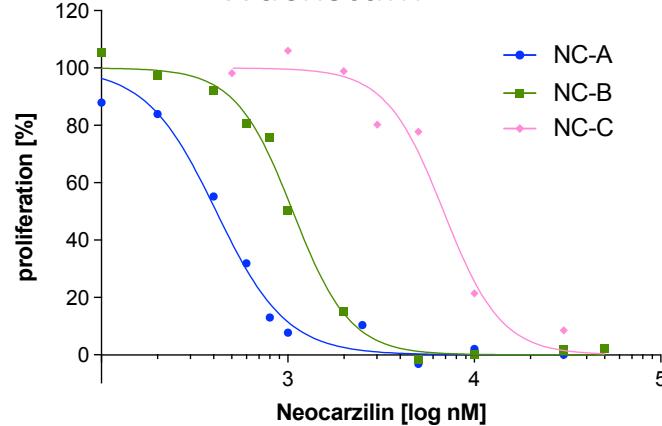


*Streptomyces
carzinostaticus*

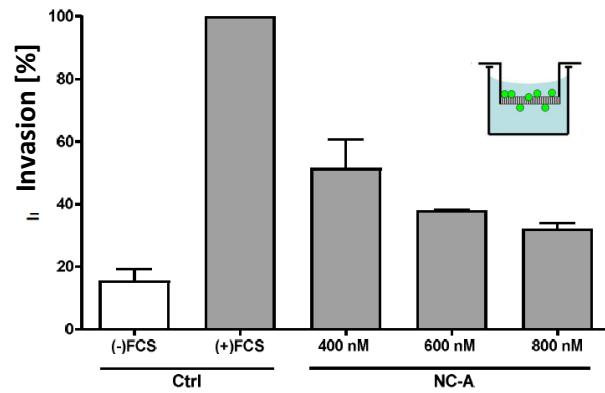


Dr. Simone Braig

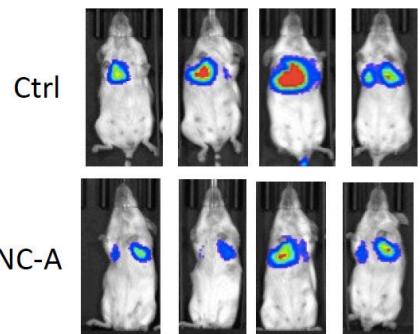
Wachstum



Invasion



Metastasis
In vivo

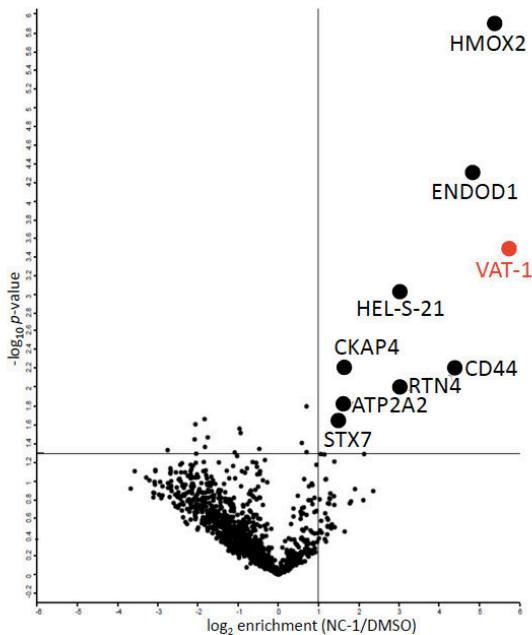


.....NEW ANTI-CANCER TARGET: VAT-1



Target Identification

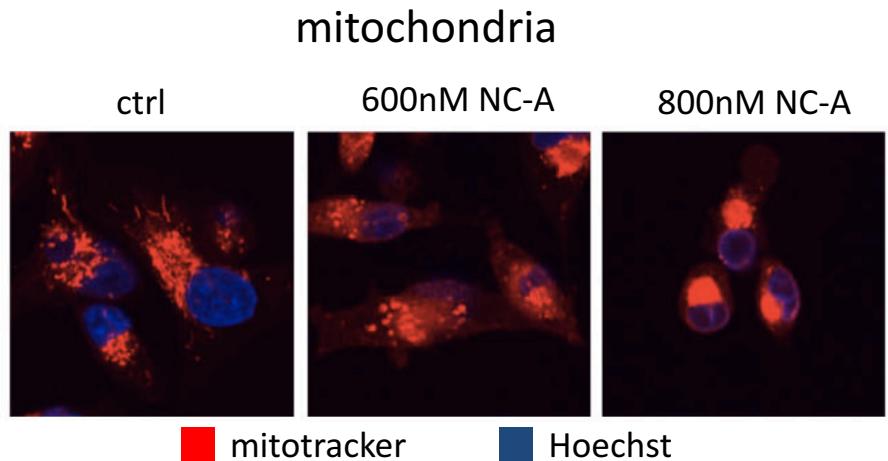
Activity-based protein profiling
(in cooperation with Prof. Sieber, TU Munich)



Function of VAT1 in cancer: ???

Working Hypothesis:

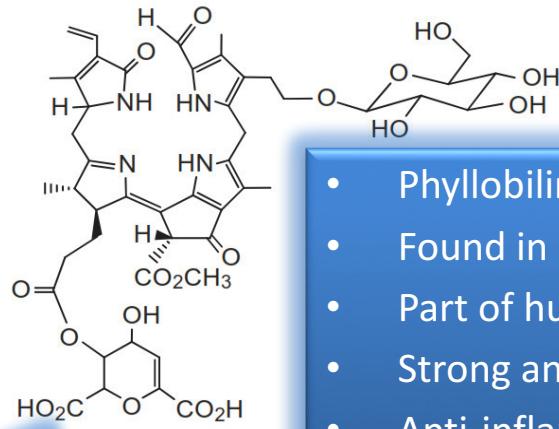
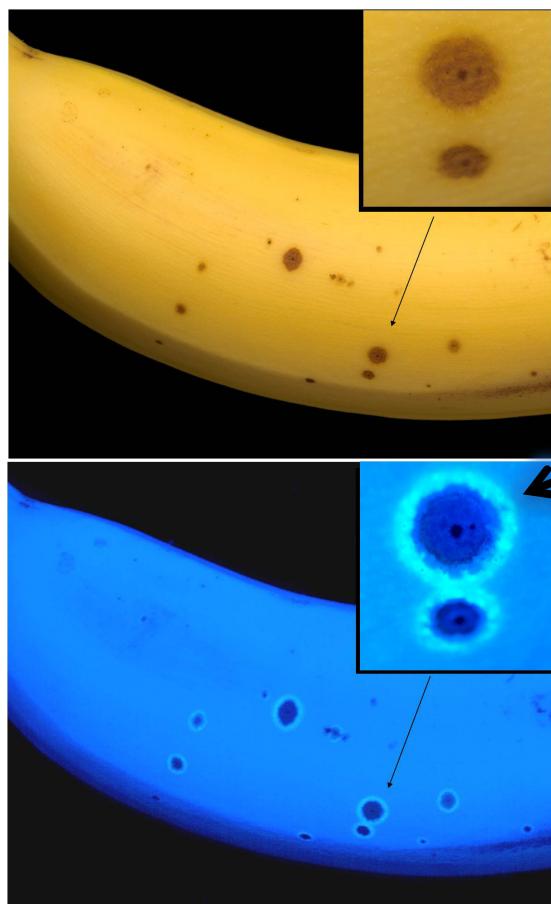
Binding of Neocarzilin to VAT1 led to mitochondrial dysfunction, thus diminishing tumor growth and metastasis.



PHYLLOBILINS - ROLE IN CANCER ?



Dr. Simone Moser



- Phyllobilins are breakdown products of chlorophyll
- Found in all higher plants
- Part of human nutrition
- Strong antioxidants
- Anti-inflammatory properties



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Bananas turn bright blue under ultra-violet light helping animals pick ripe ones

Bananas turn from yellow to bright blue under ultra-violet light helping animals decide which ones are ripe enough to eat.

Published: 7:00AM BST 08 Sep 2009

Share |



- Physiological roles?
- Cancer prevention/therapy?



THERAPEUTICAL POTENTIAL OF PHYLBILINS IN CANCER - METHODS



Natural product chemistry

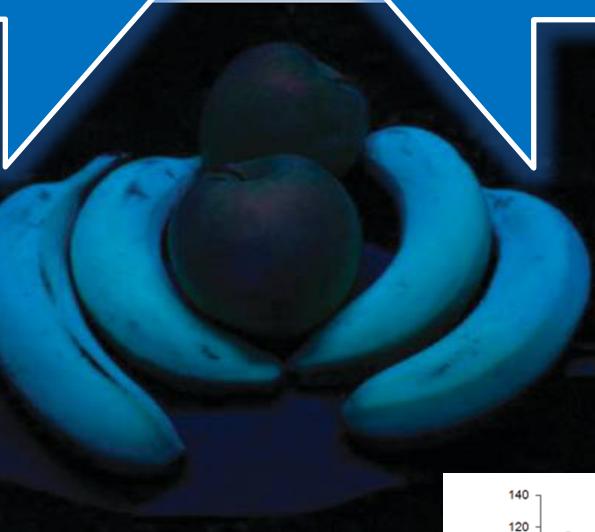
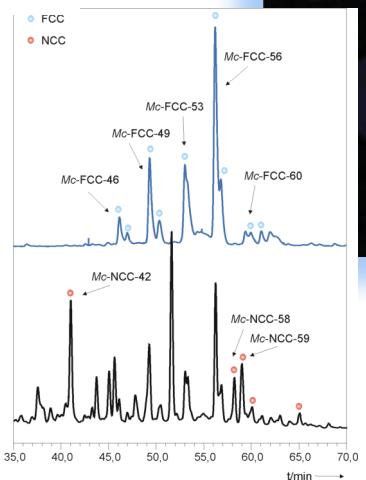
Isolation*MS*LC-MS*NMR*
Analytical chemistry*Organic synthesis

Mode of action studies

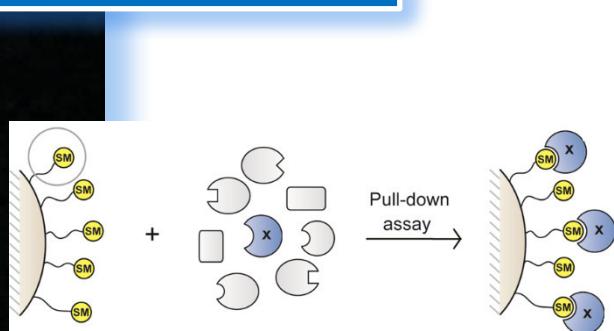
Cell models*Cloning*Protein expression*qPCR*Enzyme assays*Pull downs*Screenings



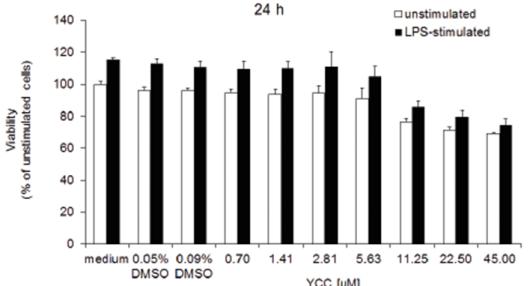
Source



Effect / phenotype



Mode of action / Target ID

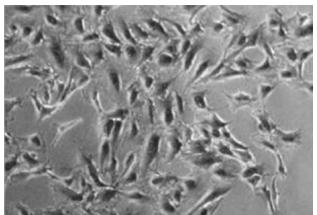


Methodology I

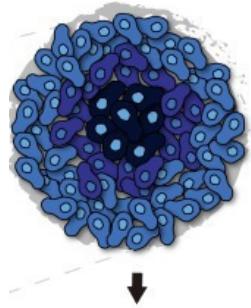
Function

Innovative
Biological
Testing

2 D and 3D cellular models

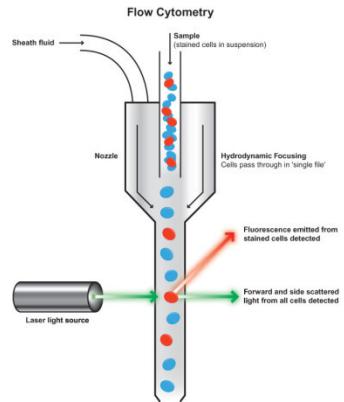


Tumor spheroids

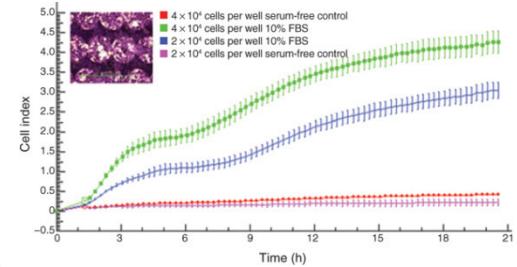
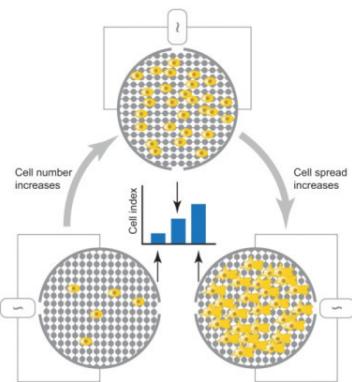


Optical microscopic
image of MCF-7 spheroid

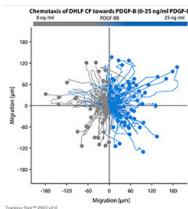
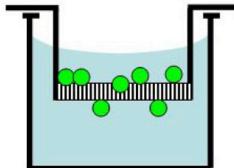
Flow cytometry



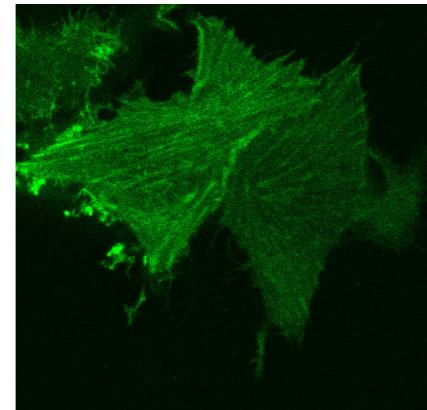
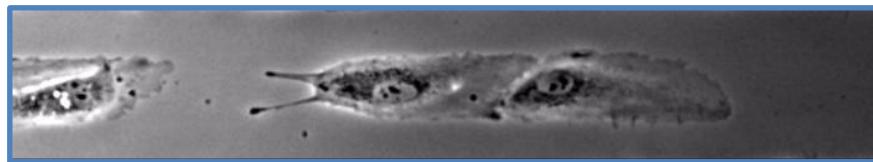
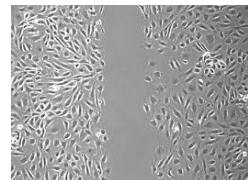
Impedance Analysis



Migration models



Live cell imaging



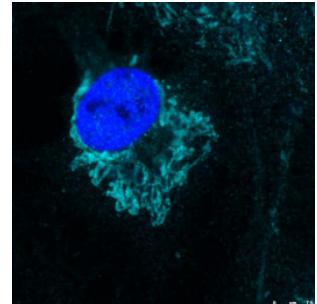
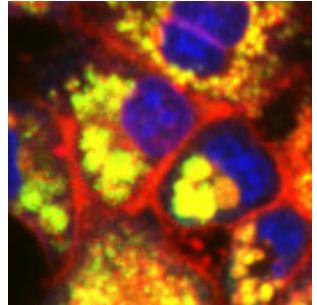
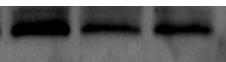
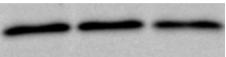
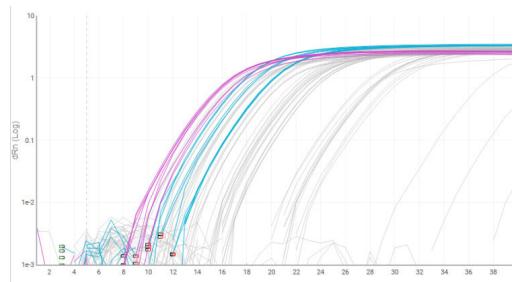
Methodology II

Mode of action

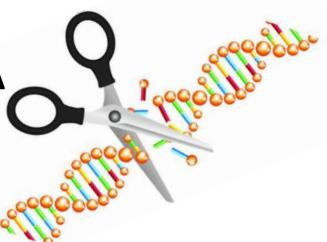
Innovative
Biological
Testing

Studies into signaling pathways

- Transcriptom analysis
- Proteom analysis/Phosphoproteom
- mRNA real-time PCR
- Protein Expression
- Microscopy



- Gene editing technology
CrispCas9, siRNA, shRNA





at our poster



Pharmaceutical Biotechnology, LMU

(Chair: Ernst Wagner)

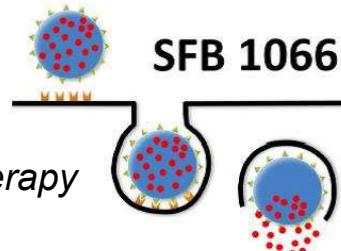
Group leaders:

Dr. Ulrich Lächelt – *Pharmaceutical Nanotechnology*
Dr. Andreas Roidl – *Cancer Chemoresistance*



DFG FOR-1406
*(Antitumoral
natural products)*

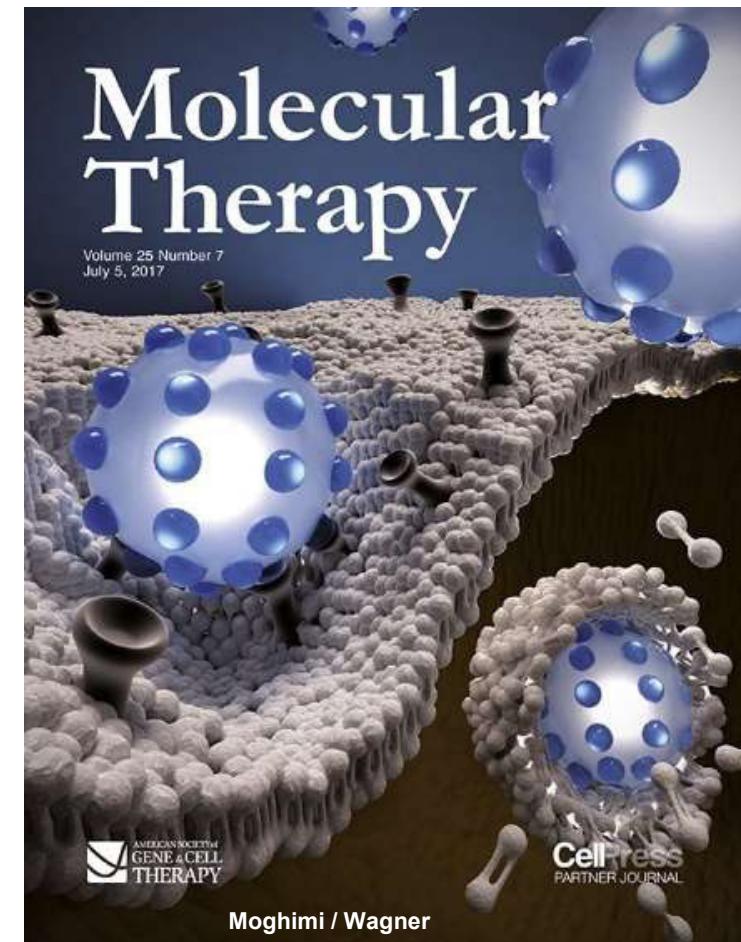
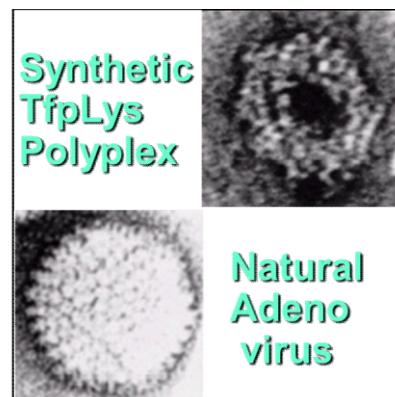
Polymer
materials
for tumor
immunotherapy
(Mainz)



- 1990: First gene therapy trial
2017: Five approved gene therapies on market
Six approved oligonucleotide drugs

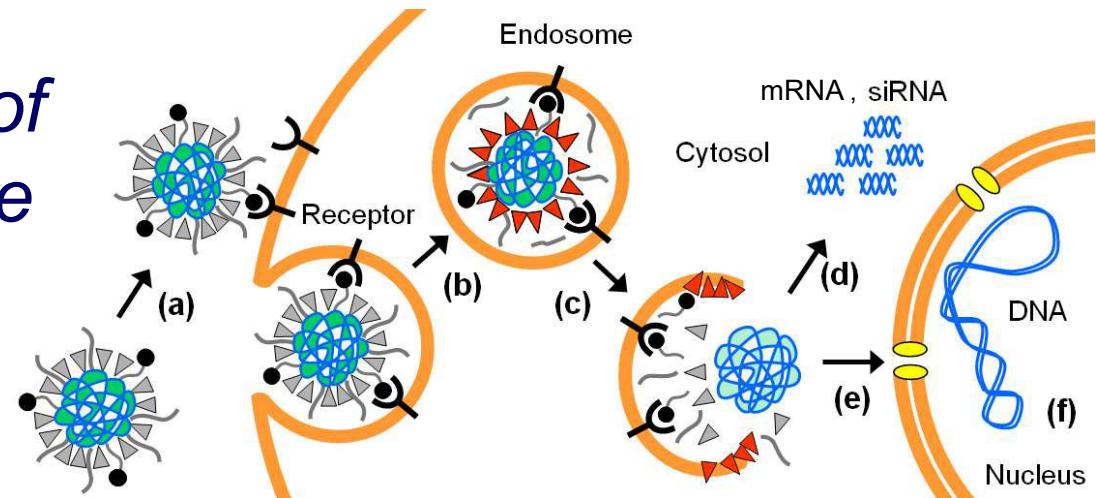


1990: Synthetic viruses



2017: Biomedical Nanoparticles

Bioinspired chemical evolution of carriers for use in nanomedicine

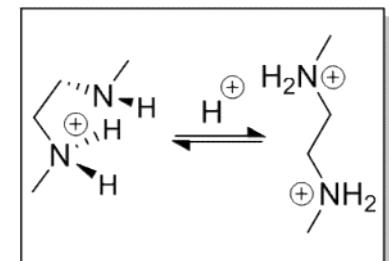


Bioresponsive carriers

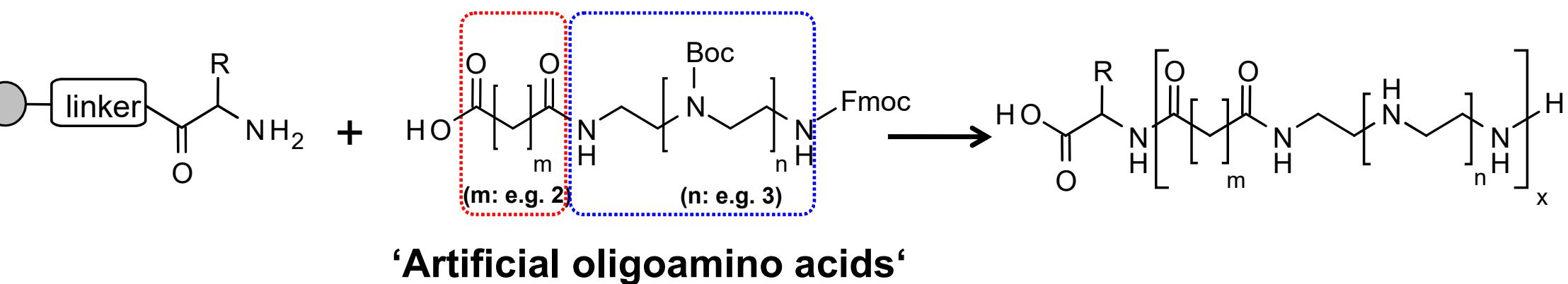
- multifunctional and chemically precise

Strategy: learn from viruses and natural evolution

- identify **chemical motifs** for delivery
- assemble them into **defined sequences**
- systematically **mutate** / shuffle
- screening → select candidates



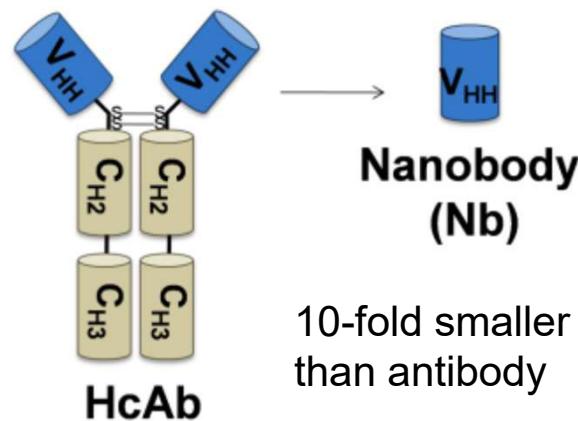
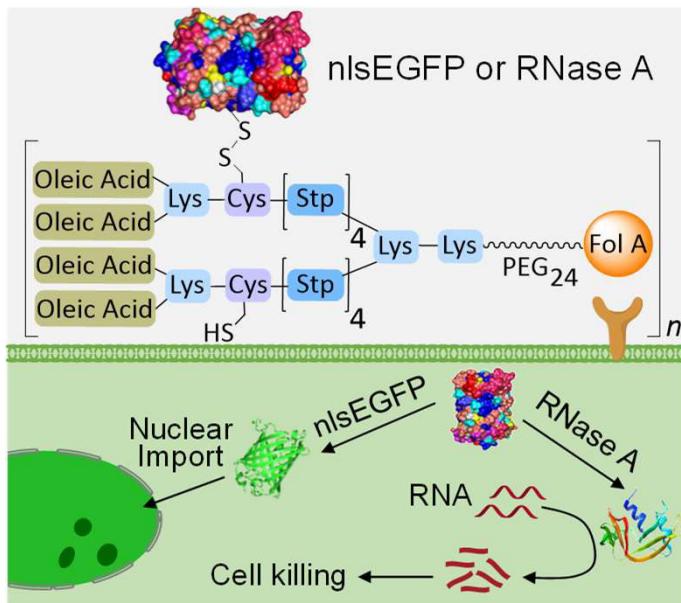
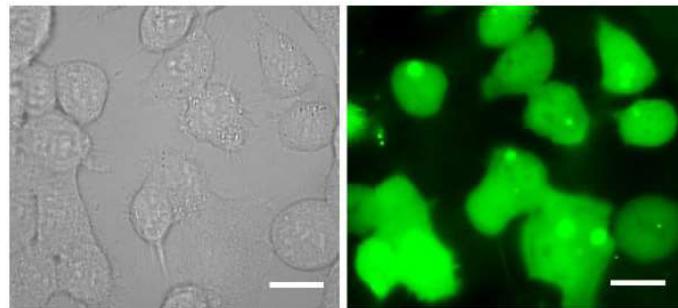
Assemble motifs into sequences: Solid phase polymer synthesis



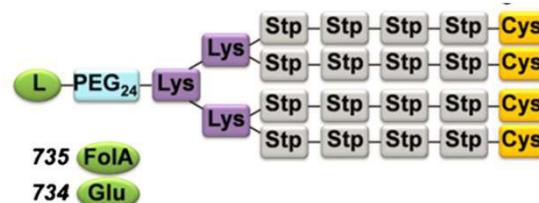
*Intracellular delivery of proteins, DNA, siRNA, miRNA, natural products :
The cargo directs the optimal carrier sequence*

Bioreversible conjugation or Caging sequences

After 48 hours



10-fold smaller
than antibody

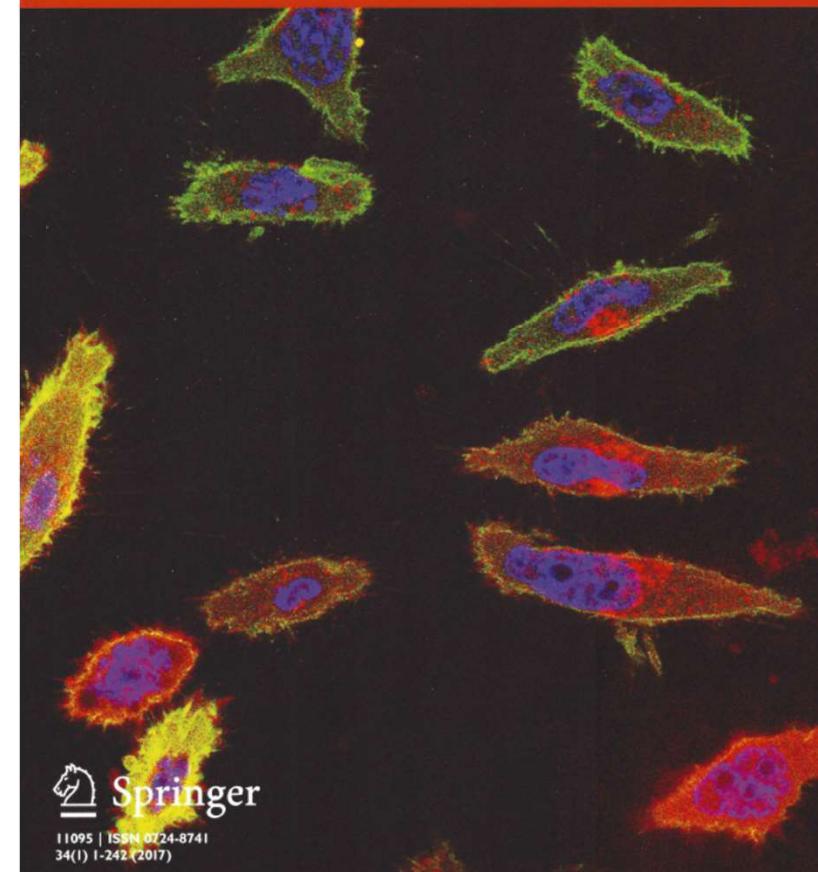


Protein delivery

Volume 34 | Number 1 | January 2017

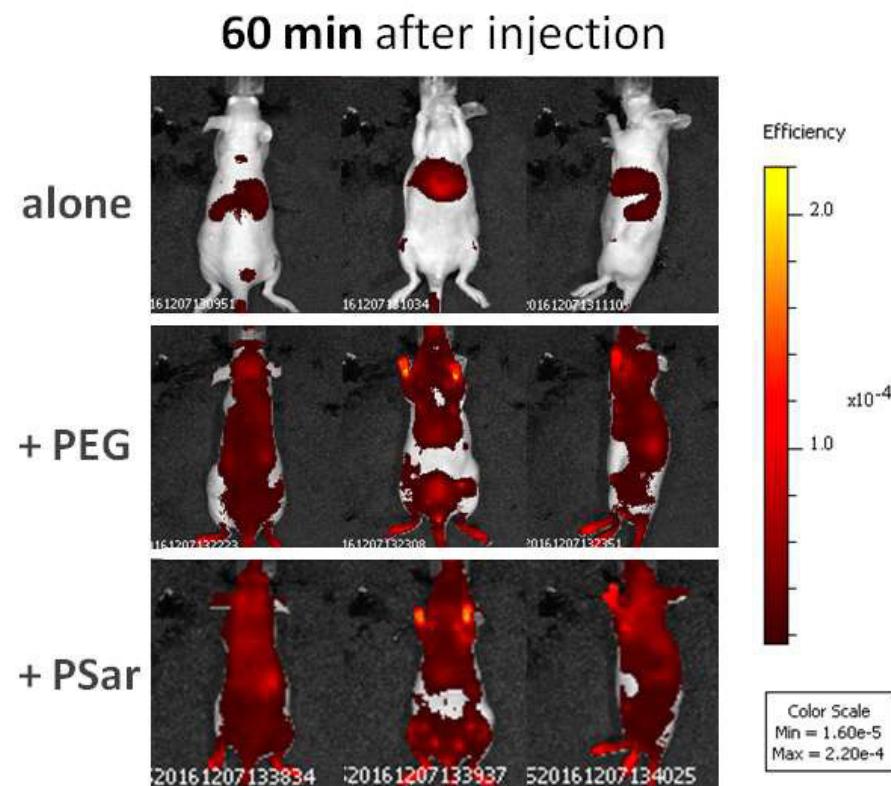
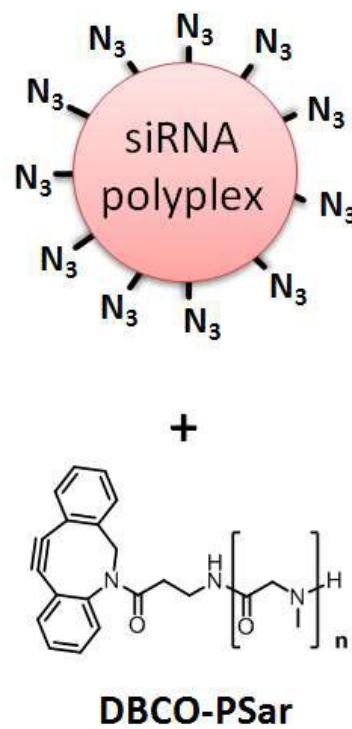
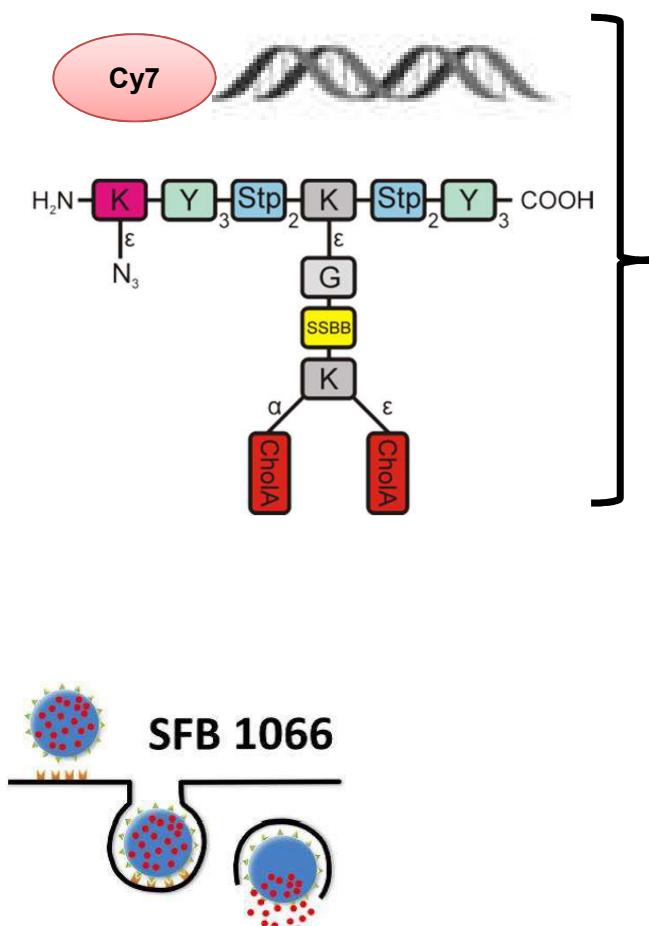
PHARMACEUTICAL
RESEARCH

aaps An Official Journal of the American Association of Pharmaceutical Scientists



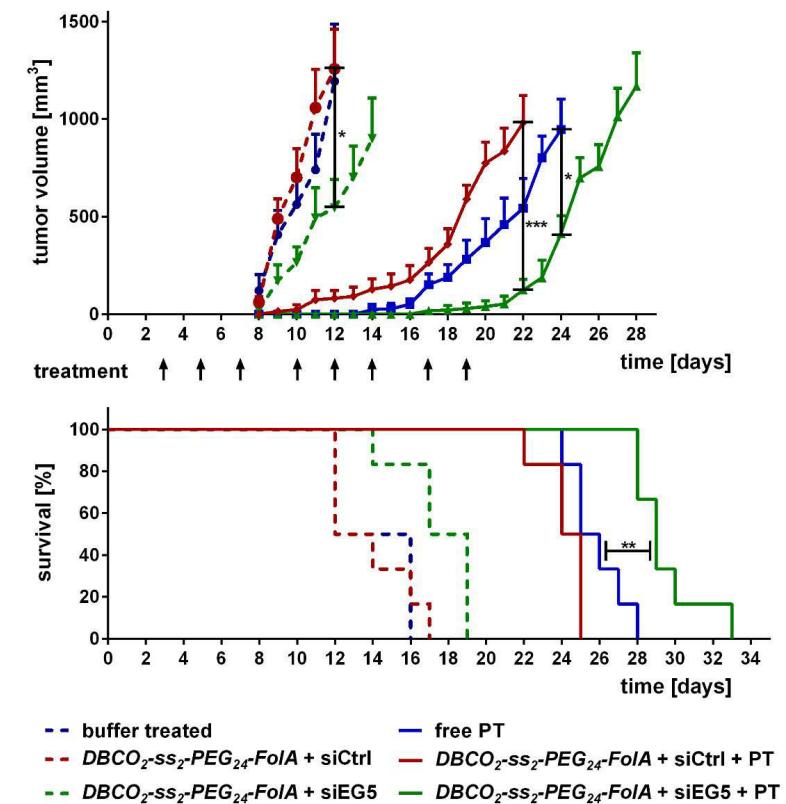
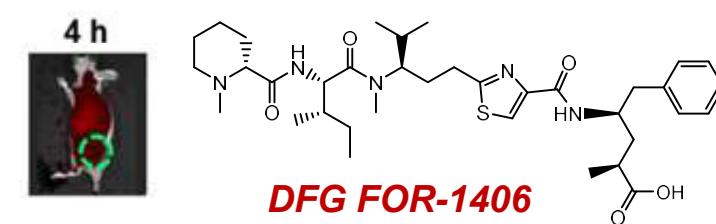
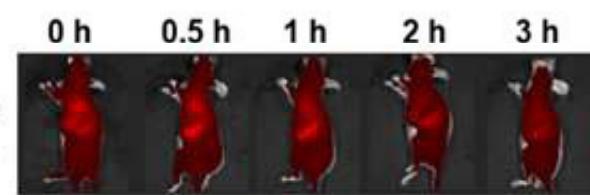
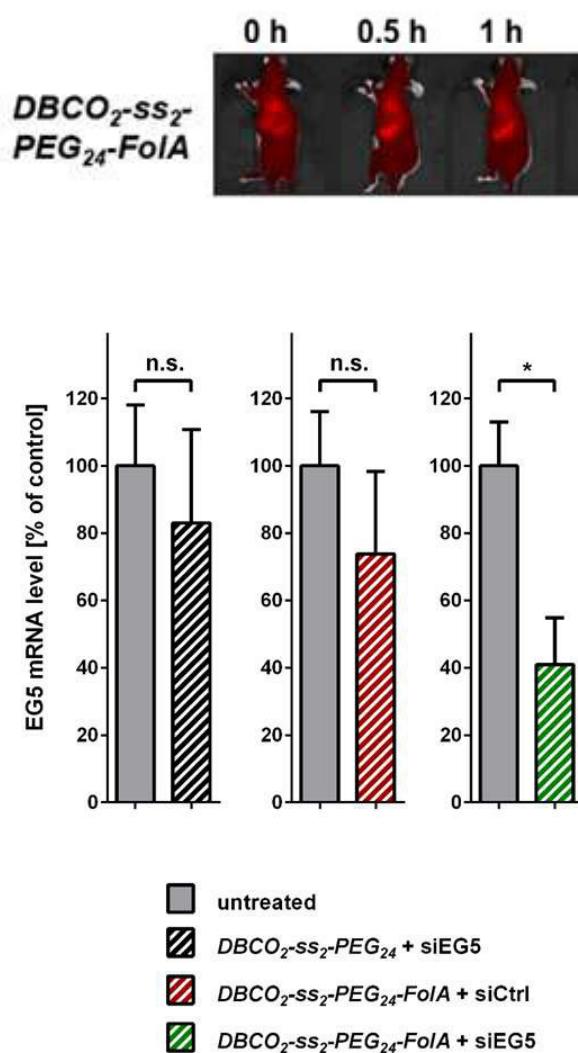
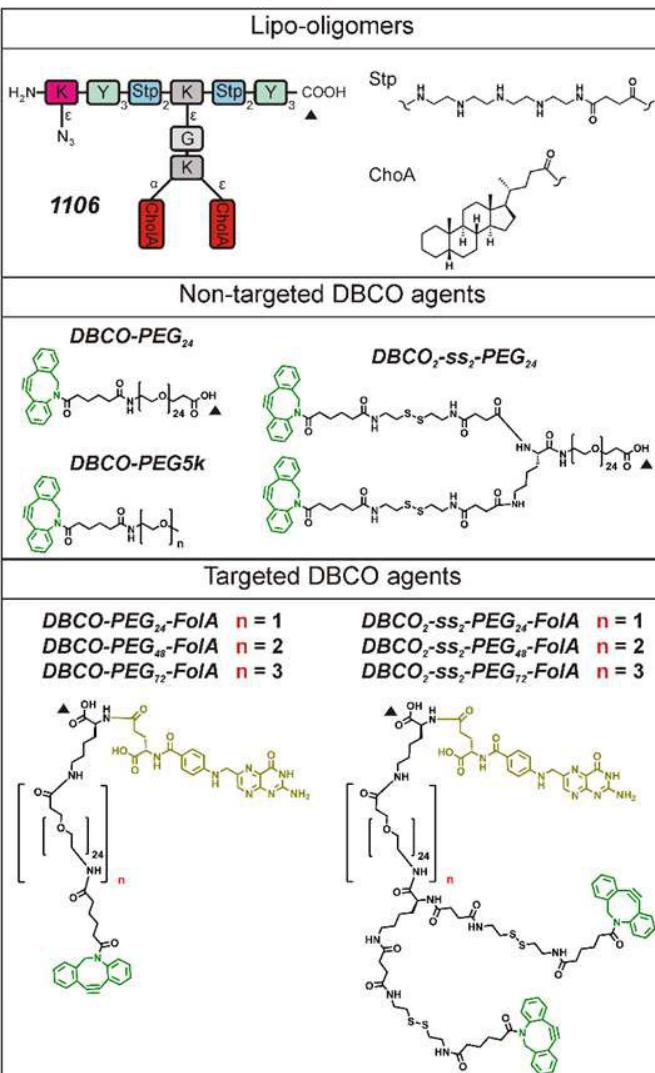
Lipo-oligomer /siRNA complexes

Click shielding & tumor targeting (cutaneous lymphoma)



Lipo-oligomer /siRNA complexes

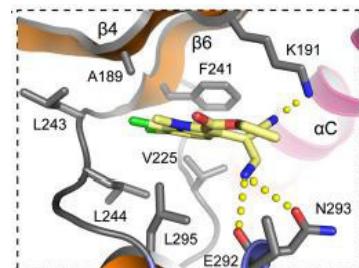
Click shielding & tumor targeting (cutaneous lymphoma)





Arbeitskreis Bracher

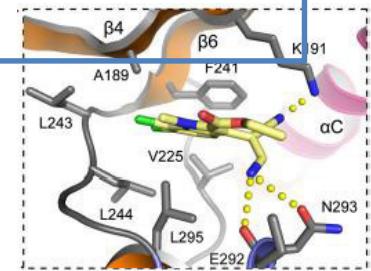
Pharmazeutische/Medizinische Chemie



Naturstoffe

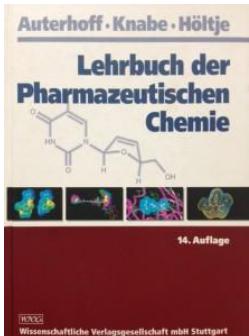


Rationales Design



neue

Leitstrukturen

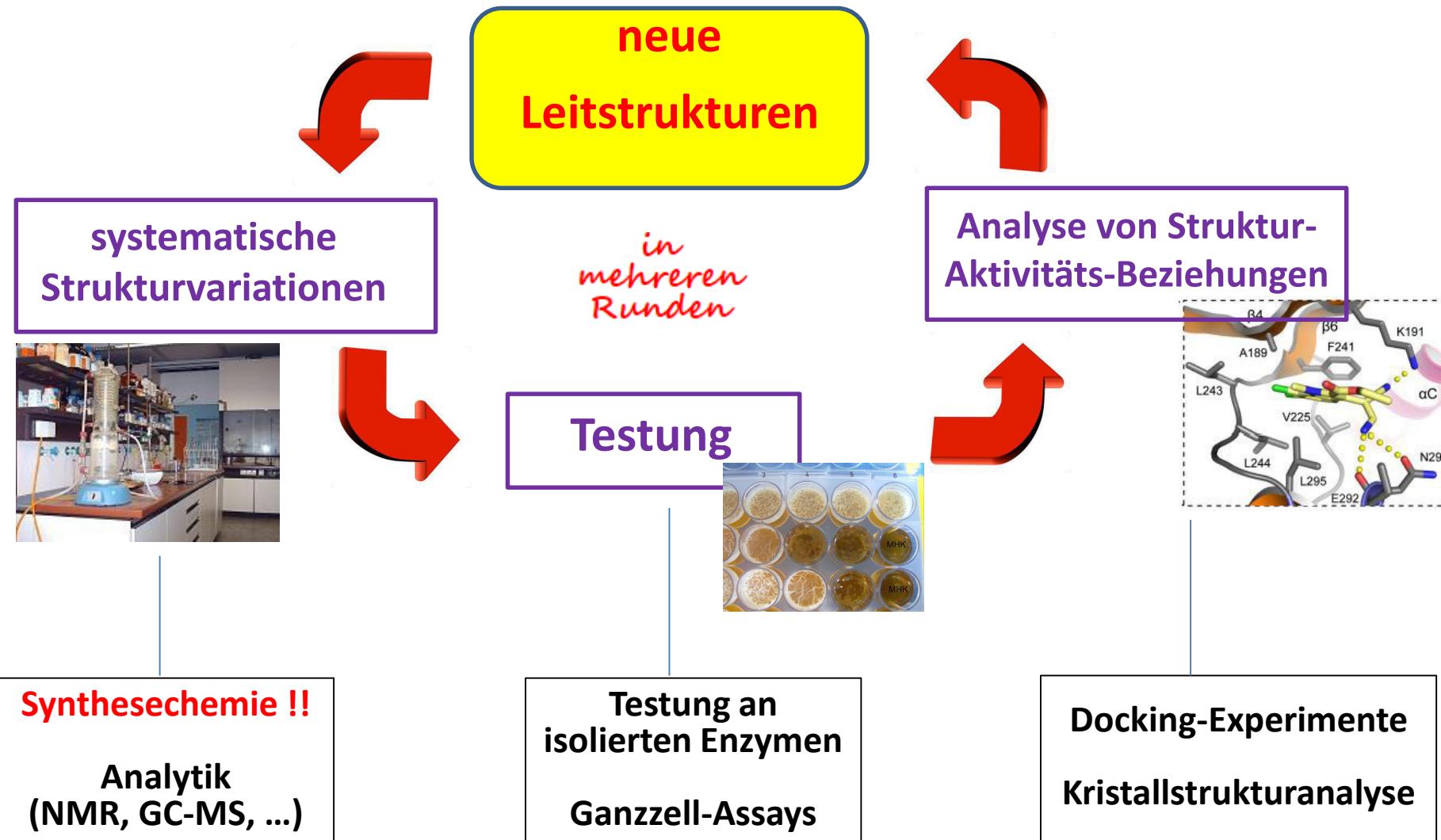


Bekannte Wirkstoffe
(target hopping)

random screening



Lead optimization



Wichtige Themengebiete

- Naturstoffsynthese
- Methodenentwicklung für neue chemische Synthesen
- Entwicklung neuer Zytostatika
- Entwicklung von **Enzyminhibitoren für epigenetische Targets** (Kinasen, Histondeacetylasen, Bromodomains, Macrodomains, DNA-Helicassen)
- Entwicklung von **Modulatoren von Ionenkanälen**

sehr viel
Heterocyclen-
Chemie

Steroidomics:

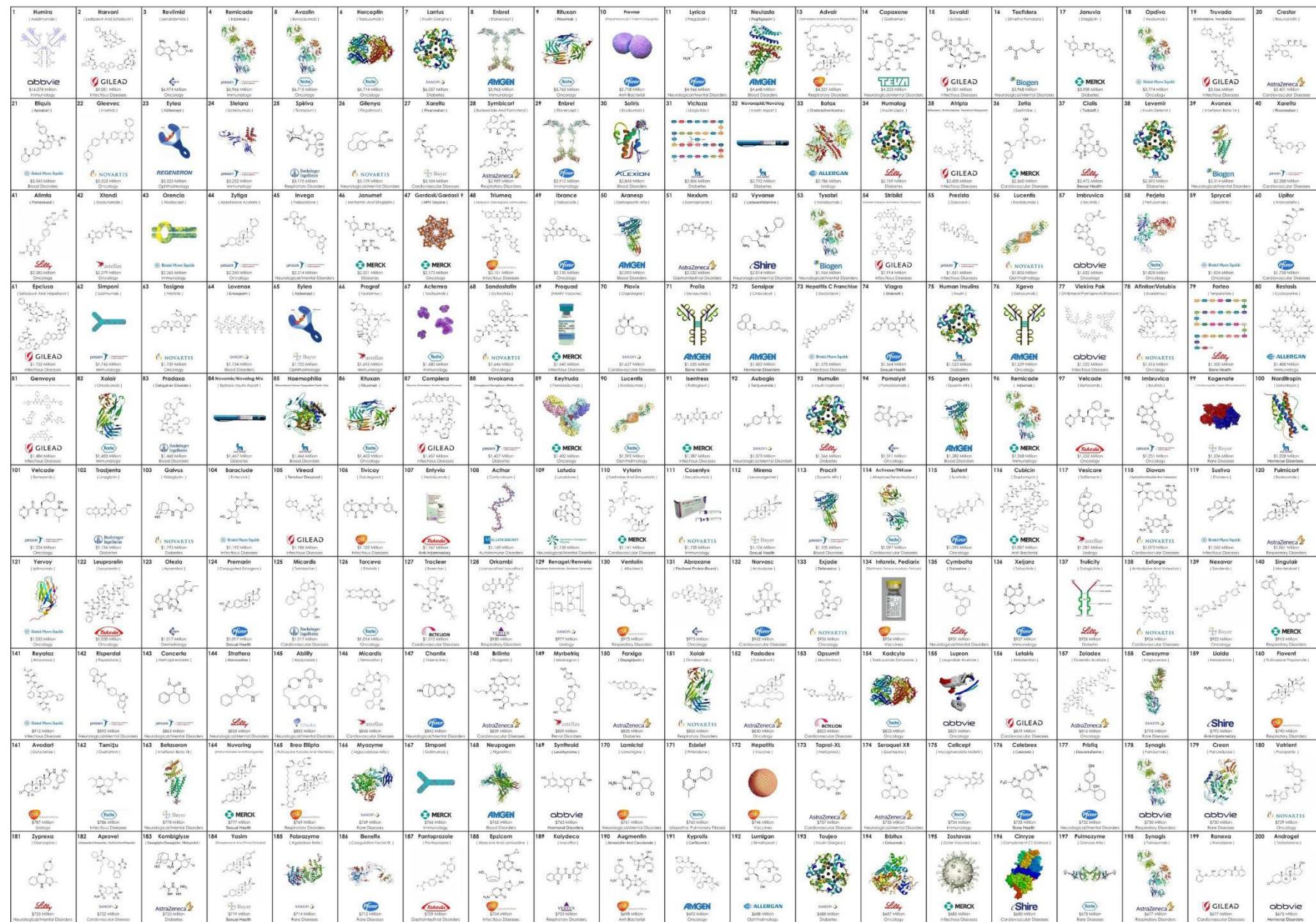
- Entwicklung von **Inhibitoren der Biosynthese von Ergosterol und Cholesterol**
- Identifizierung neuer therapeutischer Anwendungsmöglichkeiten für diese Inhibitoren
- **Sterolanalytik** (GC-MS/MS)

Assays
Analytik
Synthese

Konkrete Beispiele finden Sie auf unseren Posters

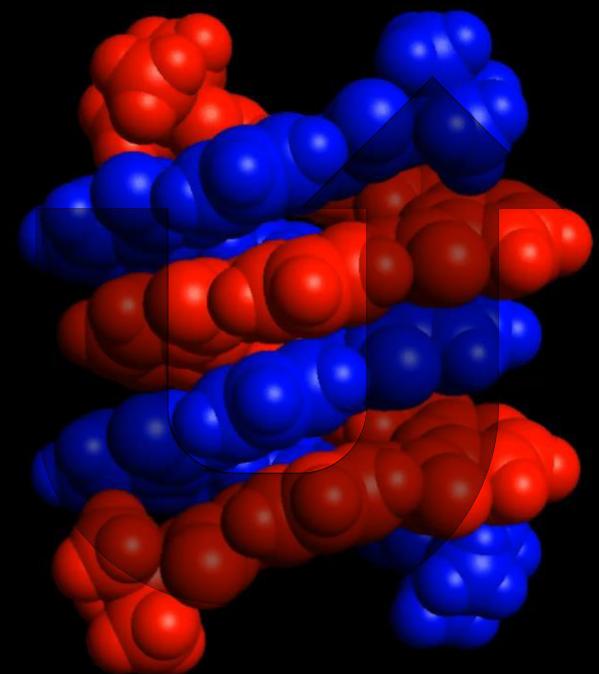
Top 200 Pharmaceutical Products by Retail Sales in 2016

Compiled and Produced by the Njardarson Group (The University of Arizona): David T. Smith, Michael D. Delost, Haziq Qureshi, Jón T. Njarðarson



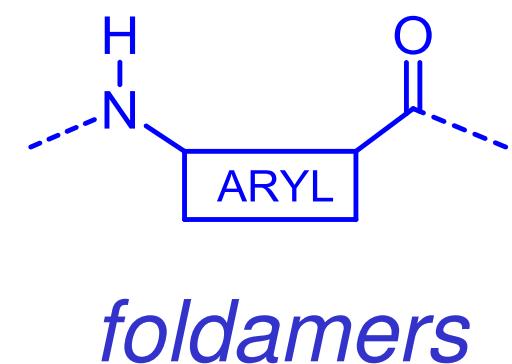
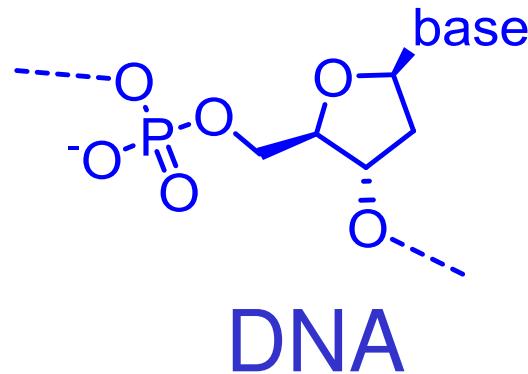
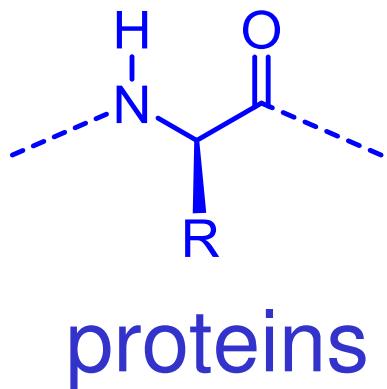
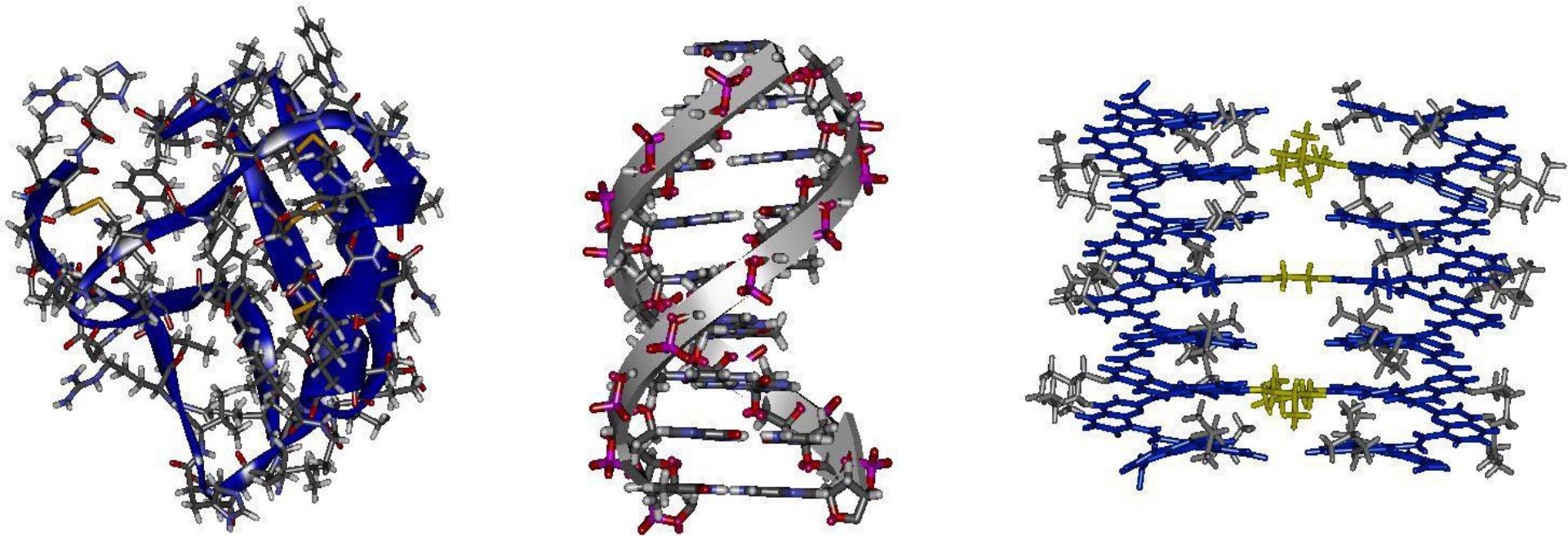
MASTERING MOLECULAR SHAPES

Prof. Ivan Huc, Dpt. Pharmazie, Ludwig-Maximilians-Universität, Munich



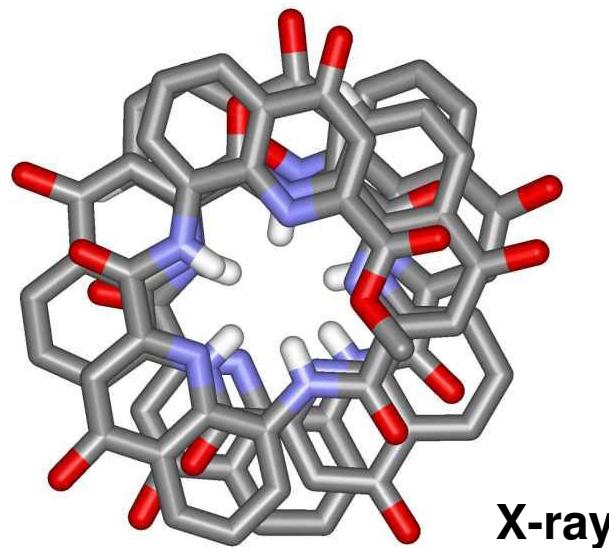
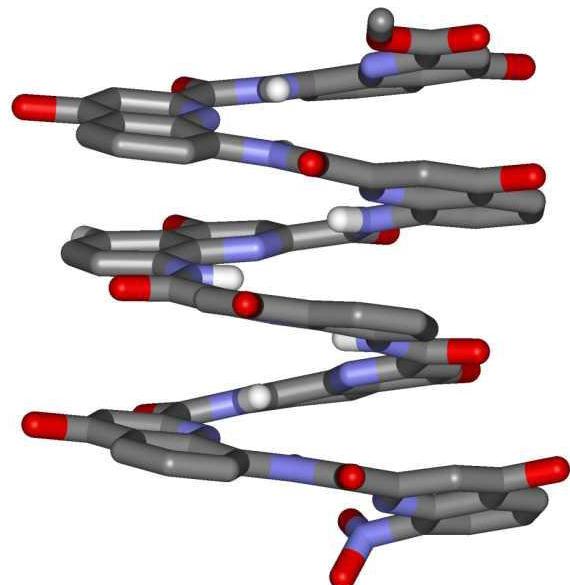
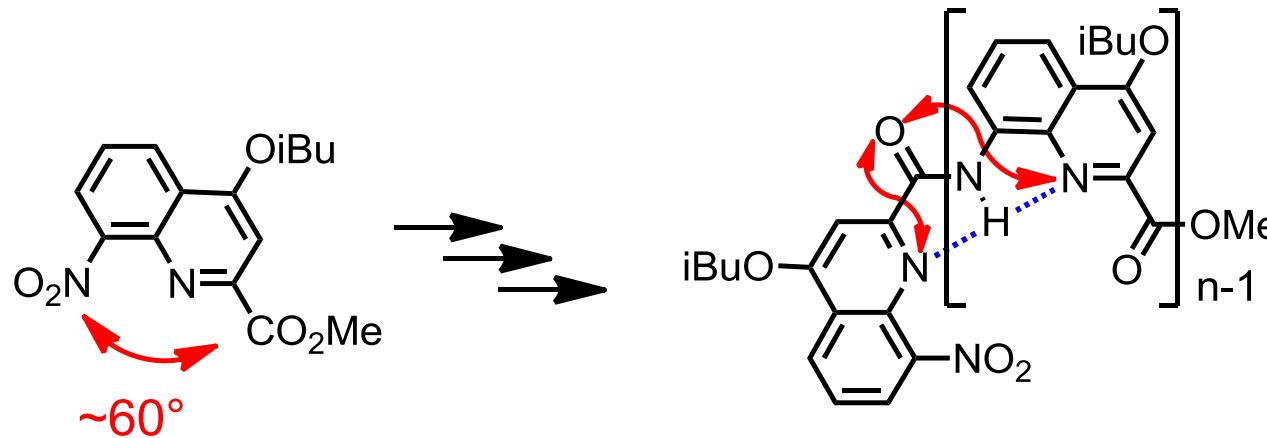
<https://huc.cup.uni-muenchen.de/>

Molecular backbones and body languages



Exploring the benefits of differences

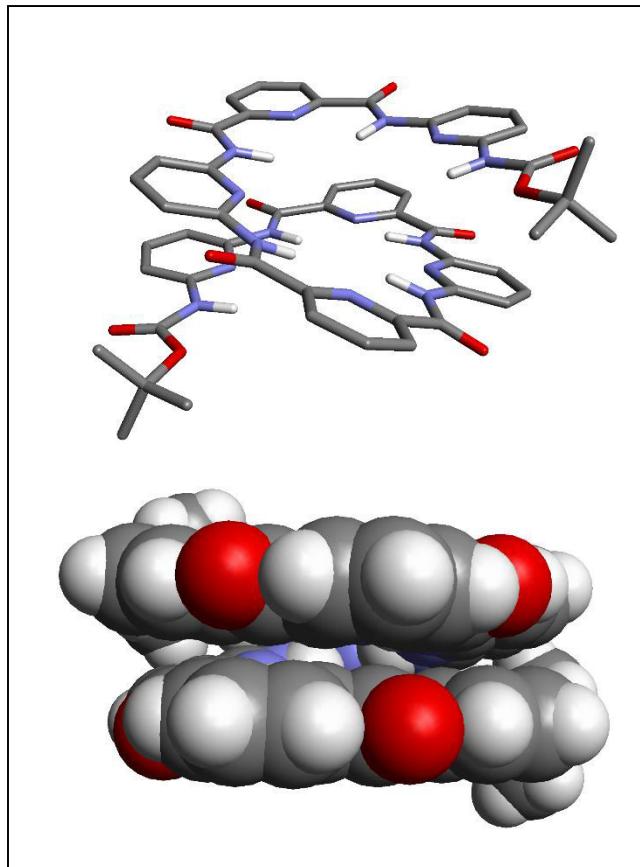
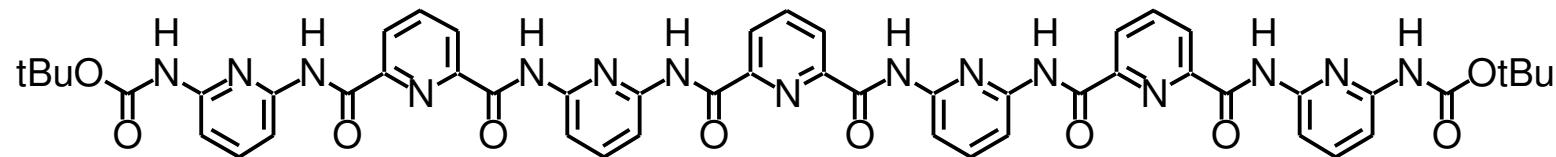
Local conformational preferences induce folding



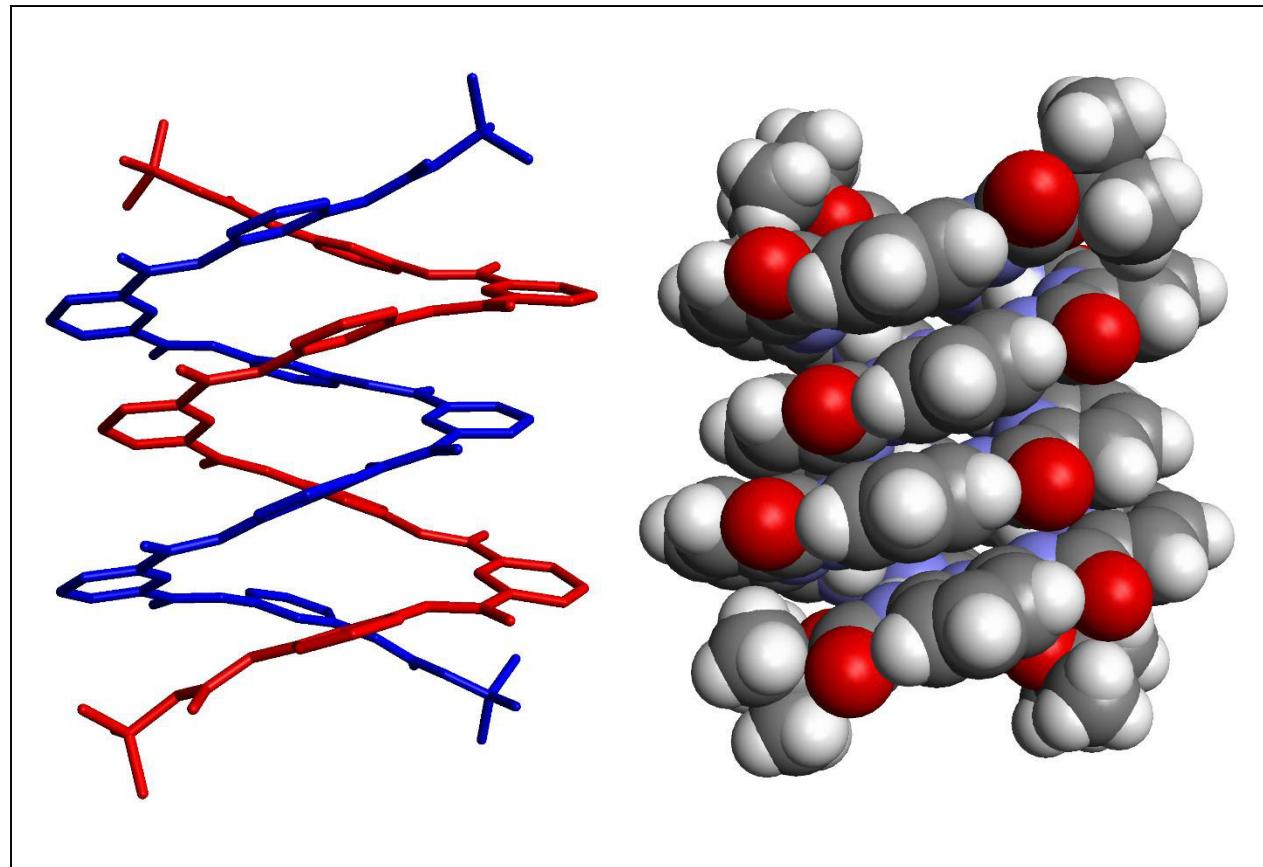
Parameters:
pitch 3.5 Å
2.5 units/turn

NO DENATURATION
 $\Delta G^\ddagger = 102 \text{ kJ/mol}$

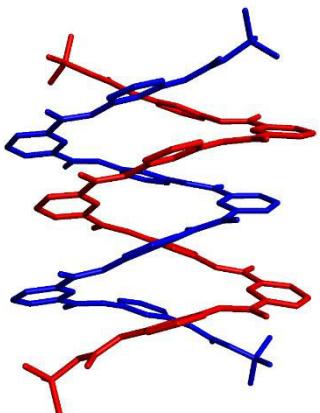
H. Jiang... *J. Am. Chem. Soc* 2003, 125, 3448
T. Qi, T. Deschrijver... *Nat. Protoc.* 2013, 8, 693



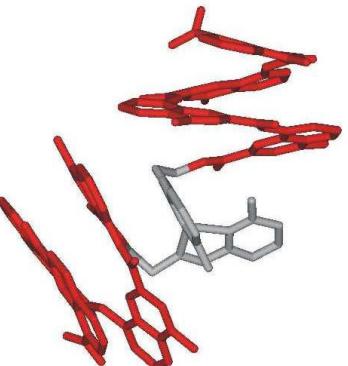
Crystals from dmso/CH₃CN



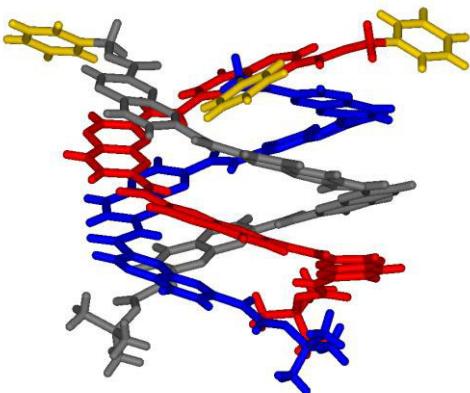
Crystals from ΦNO_2 /heptane



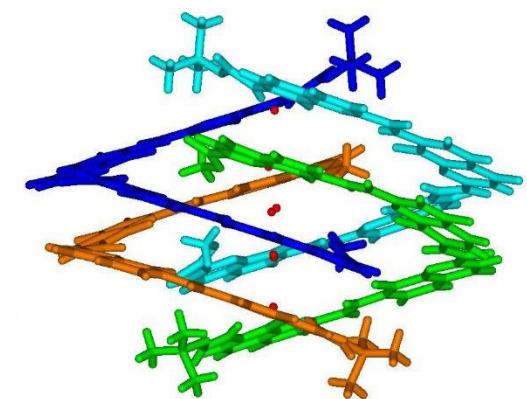
Double Helices
Nature 2000, 407, 720



Helices at an angle
CEJ 2008, 14, 7140

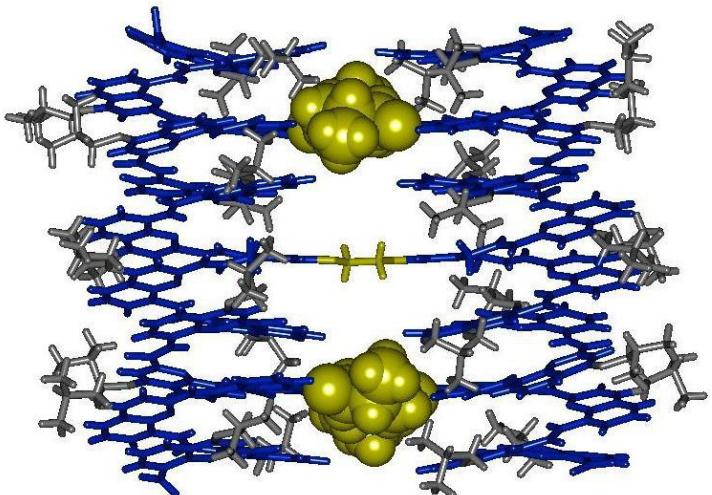


Triple helices
ACIE 2010, 49, 1778

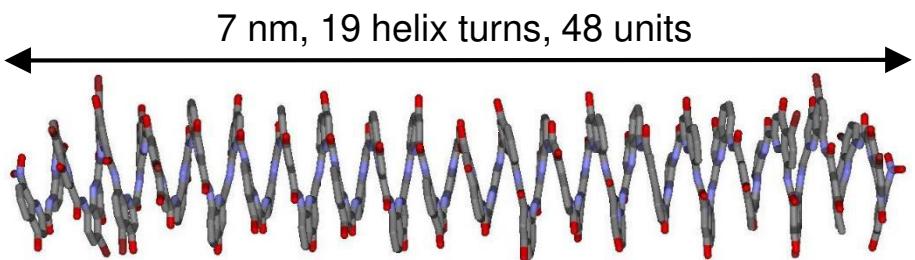


Quadruple helices
ACIE 2008, 47, 1715

A vast chemical space

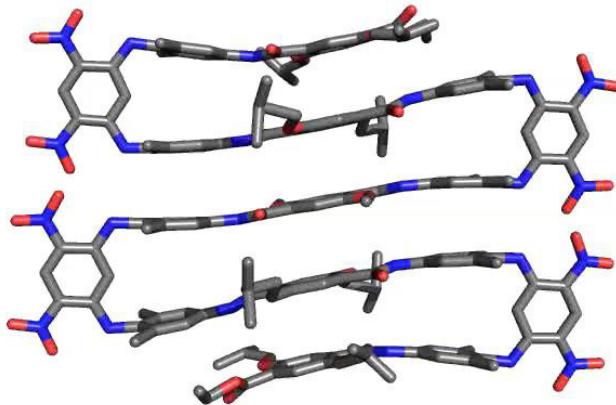


Tertiary-like folds - JACS 2011, 133, 3165

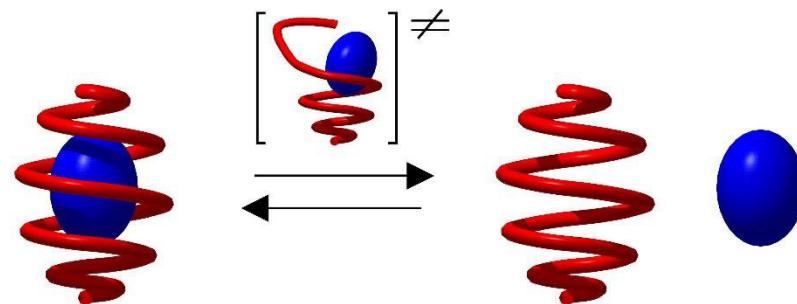


Nanosized helices - JACS 2009, 131, 8642

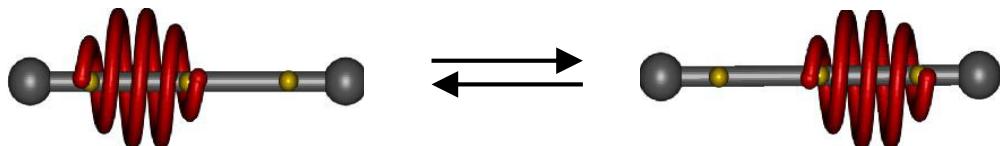
Aromatic Sheets
JACS 2014, 136, 2168



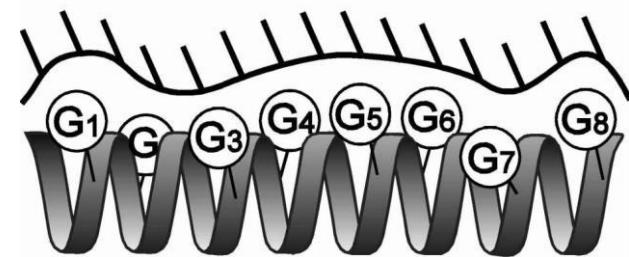
New shapes for molecular recognition



Endomolecular Recognition



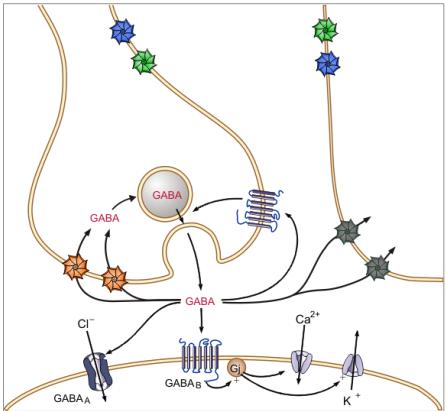
target protein surface



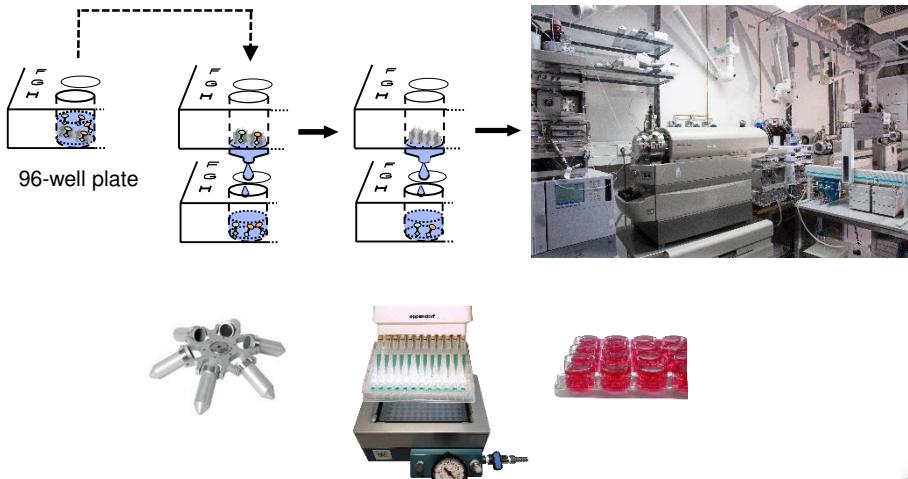
**Exomolecular
Recognition**



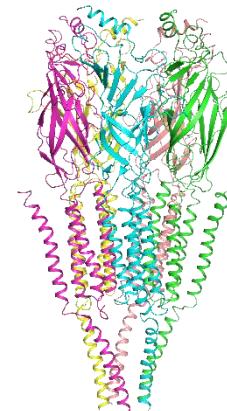
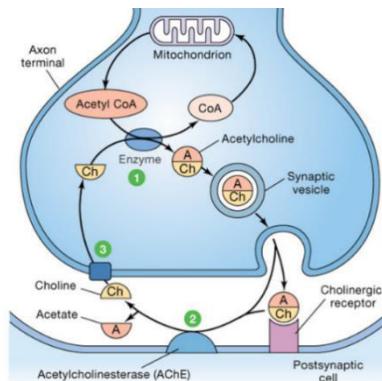
Inhibitoren der GABA-Transportproteine



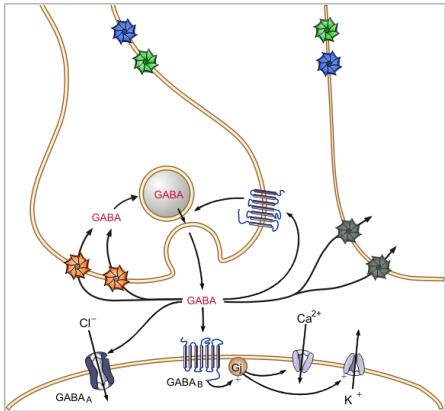
MS Bindungsstudien



Resensitizer nikotinischer Acetylcholinrezeptoren



Inhibitoren der GABA-Transportproteine



hGAT1

Vorkommen im ZNS

Neocortex, hippocampus,
Cerebellum, Hirnstamm, Rückenmark

Indikationsgebiete,

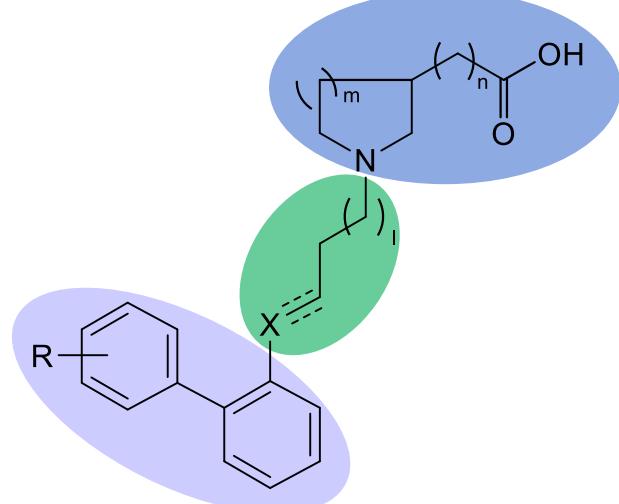
Epilepsie, neuropathischer Schmerz, Angst, Panikattacken



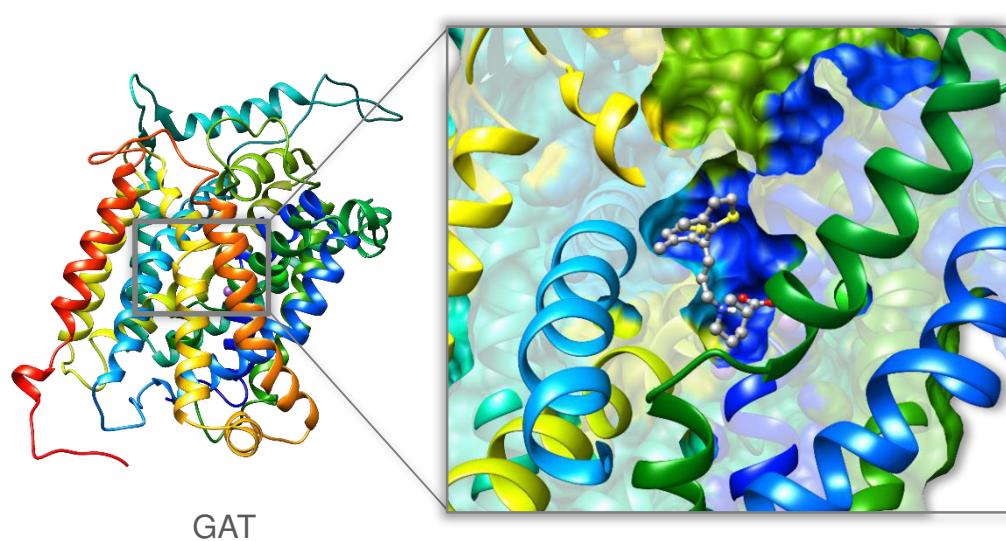
hGAT3

Thalamus, Hypothalamus,
Hirnstamm, Rückenmark

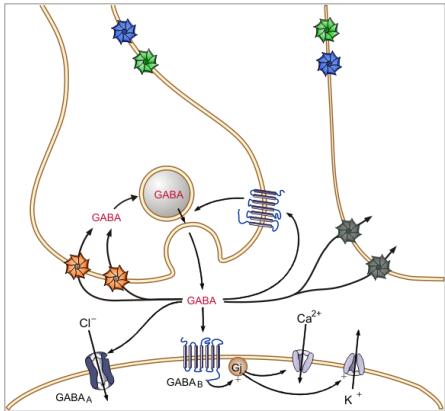
Fragmentbasiertes Design



Strukturbasiertes Design



Inhibitoren der GABA-Transportproteine



hGAT1

Vorkommen im ZNS

Neocortex, hippocampus,
Cerebellum, Hirnstamm, Rückenmark

Indikationsgebiete,

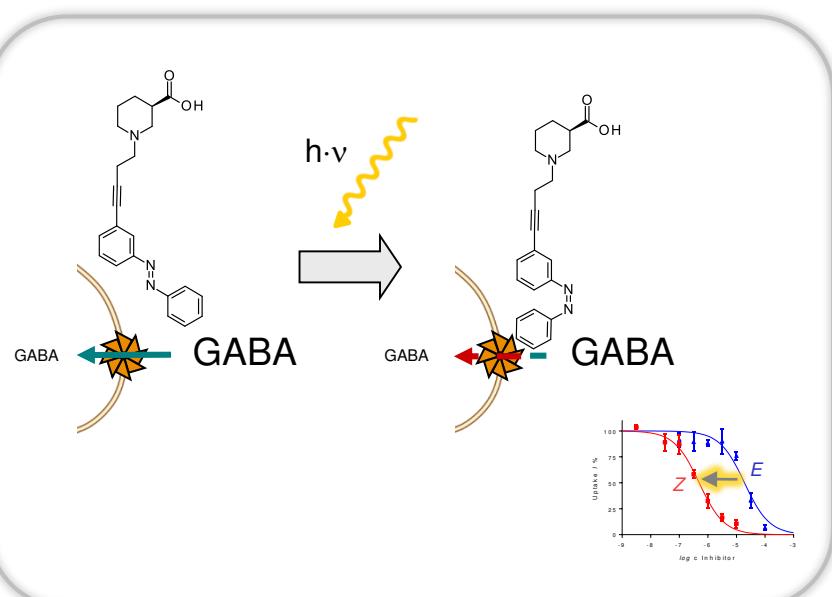
Epilepsie, neuropathischer Schmerz, Angst, Panikattacken



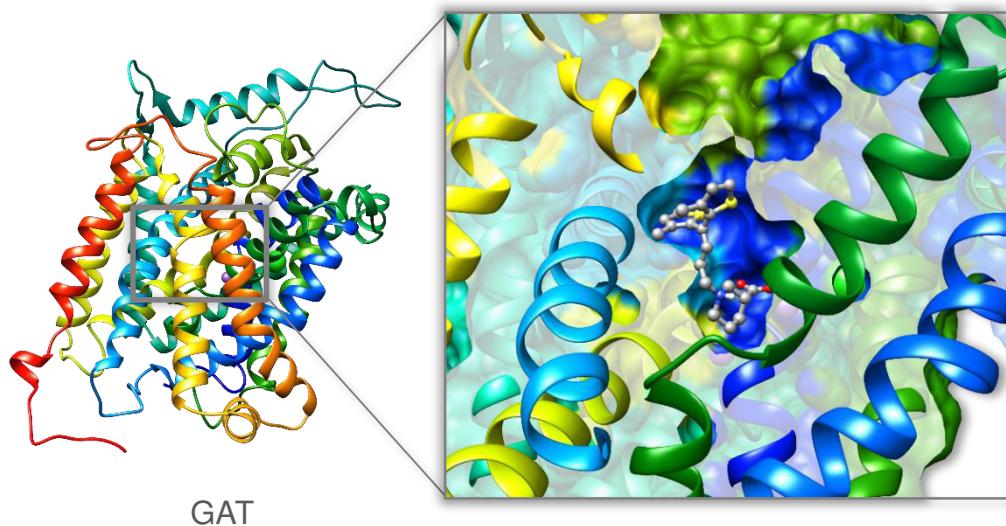
hGAT3

Thalamus, Hypothalamus,
Hirnstamm, Rückenmark

Fragmentbasiertes Design



Strukturbasiertes Design



Radioligand-Bindungsstudien

Stärken

- breit anwendbar
- exakte und verlässliche Daten
- Goldstandard

Schwächen

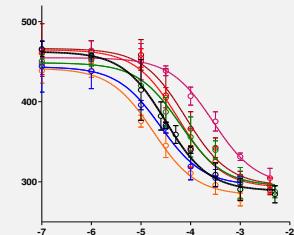
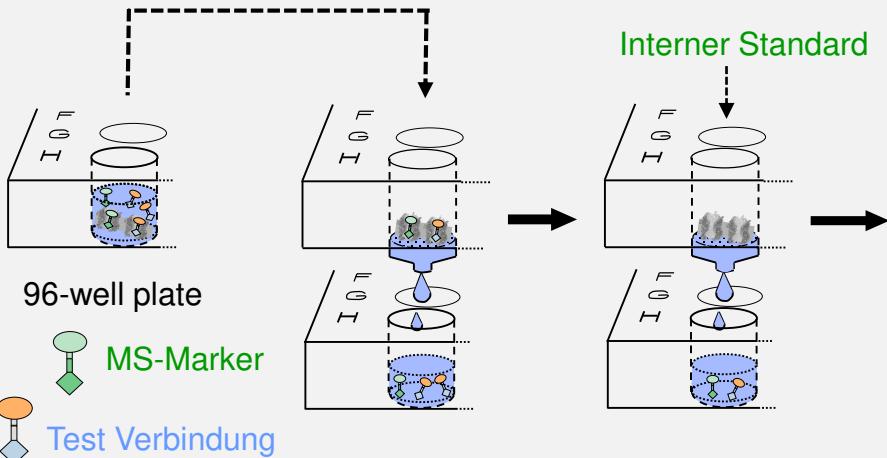
- Synthese von Radioliganden teuer
- Sicherheitsvorkehrungen erforderlich (S1-Bereich)
- Umweltbelastung, radioaktiver Abfall

MS Bindungsstudien

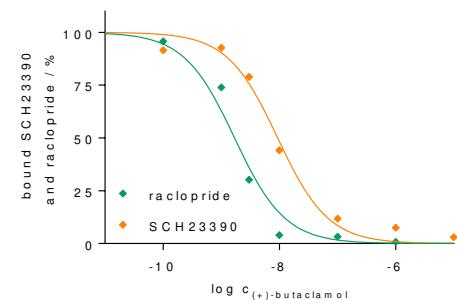
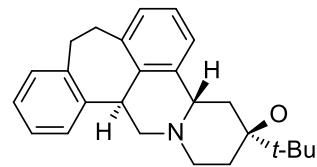
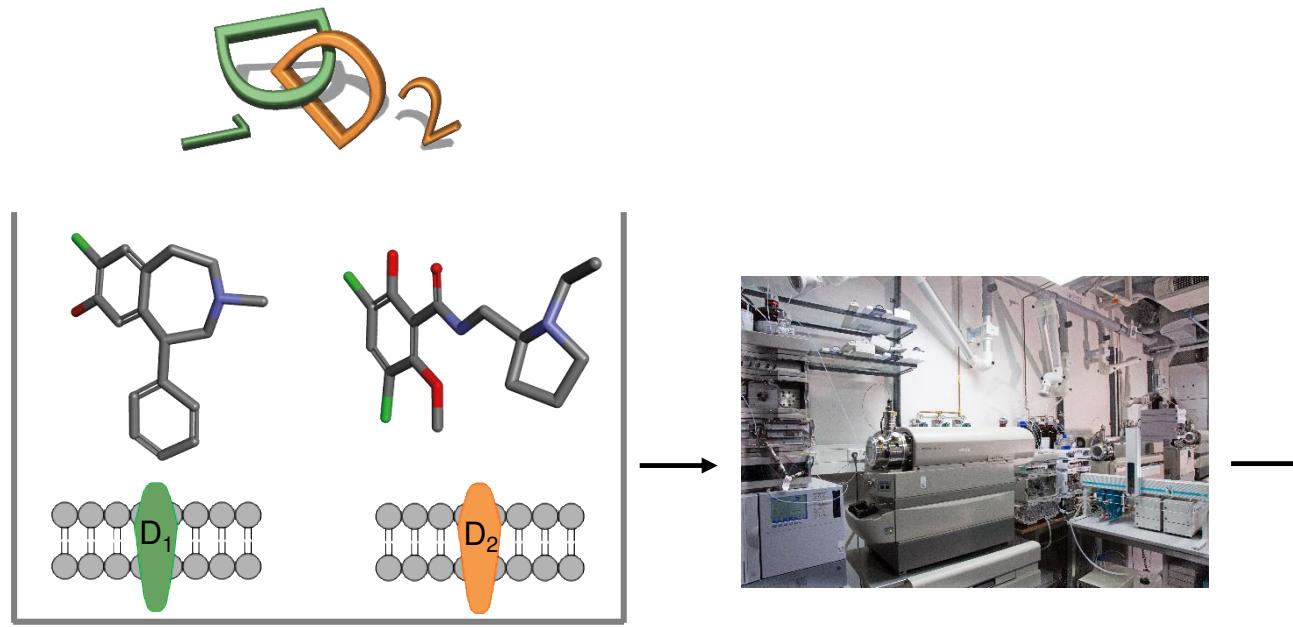
Stärken

- ✓
- ✓

- leicht durchführbar
- keine Radioaktivität



Simultane Multiple MS Bindungsstudien

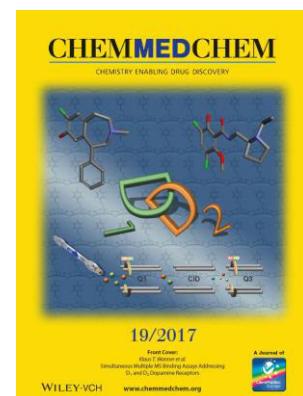


D₁

D₂

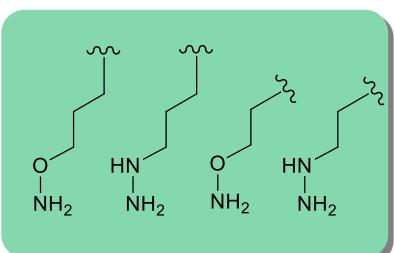
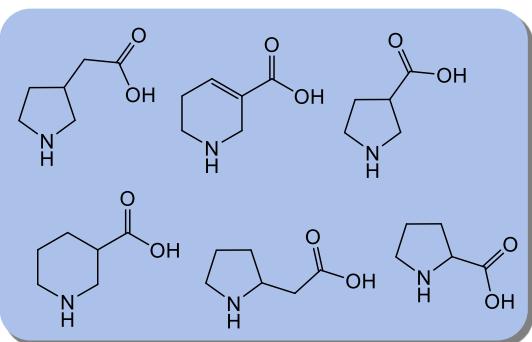
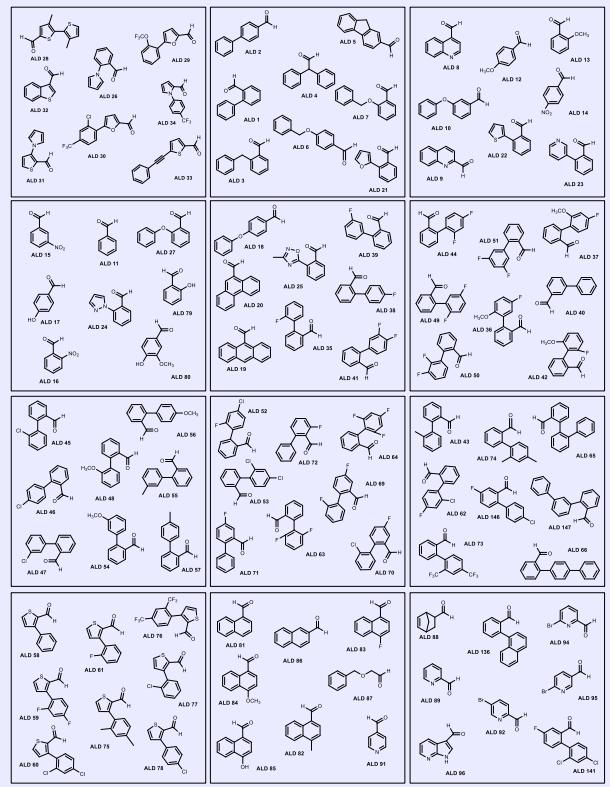
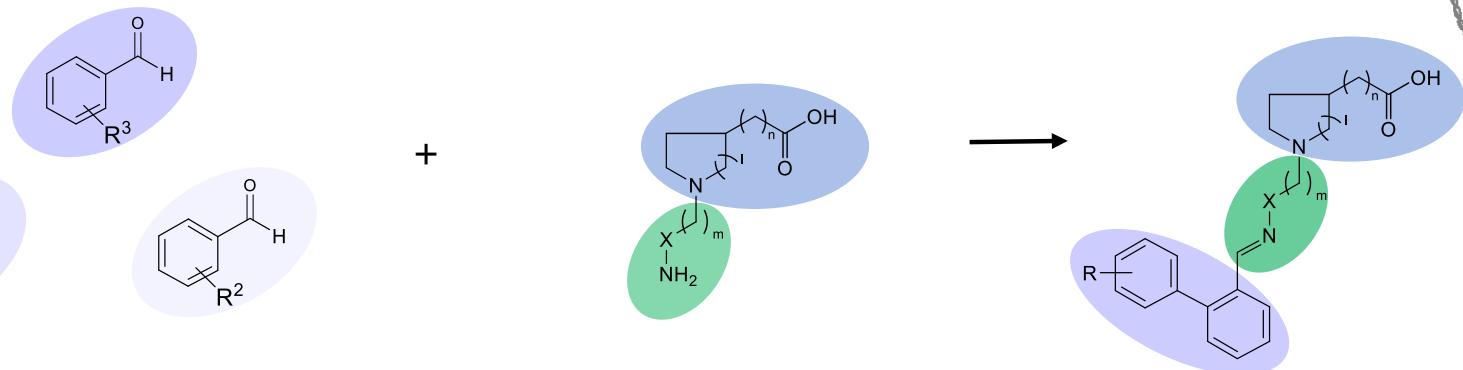
D₁ Rezeptor **Agonisten**
D₂ Rezeptor **Antagonisten**

hypertensive Krise
Schizophrenie, Erbrechen



M. Schuller, G. Höfner, K.T. Wanner, "Simultaneous Multiple MS Binding Assays addressing D₁ and D₂ Dopamine receptors", *ChemMedChem* 2017, 12, 1585-1594

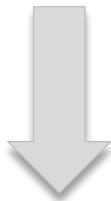
Screening Pseudostatischer Substanzbibliotheken



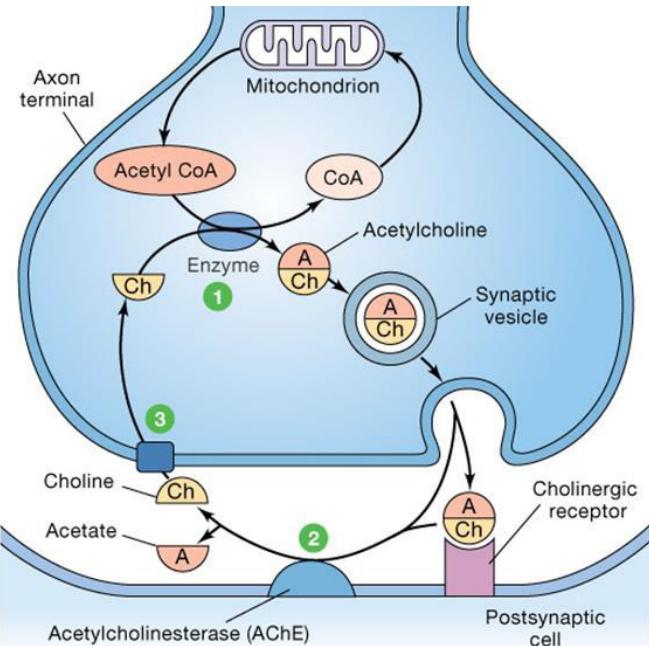
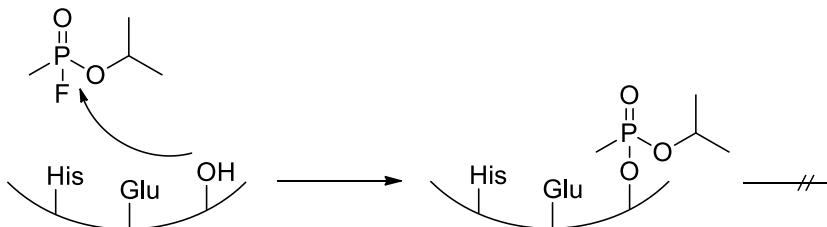
M. Sindelar, T. A. Lutz, M. Petrera, K.T. Wanner, "Focused Pseudostatic Hydrazine Libraries Screened by Mass Spectrometry Binding Assay – Optimizing Affinities towards γ -Aminobutyric Acid Transporter 1", *J. Med. Chem.*, 2013, 56, 1323-1340.



Organophosphatvergiftung



Inhibierung der Acetylcholinesterase

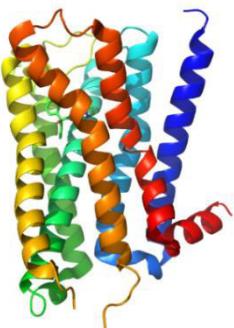


Akkumulation von Acetylcholin
im synaptischen Spalt -> cholinerge Krise

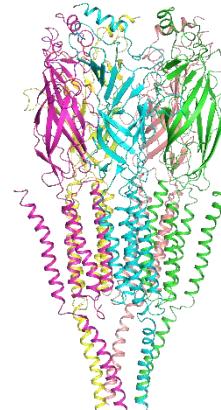


Akkumulation von Acetylcholin im synaptischen Spalt -> cholinerge Krise

Muskarinischer Acetylcholinrezeptor



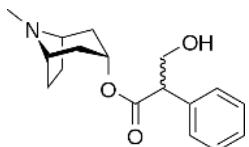
Nikotinischer Acetylcholinrezeptor



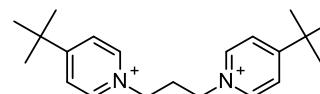
Desensitierung

Therapeutische Ansätze

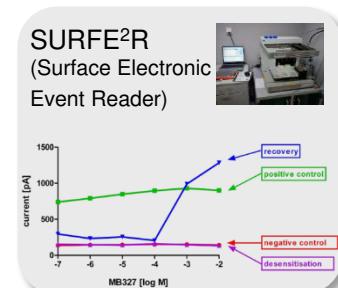
Muskarinrezeptor-Antagonisten,
z.B Atropin



Oxime für Reaktivierung der AChE
oder „Resensitizierung“
Modellverbindung MB327

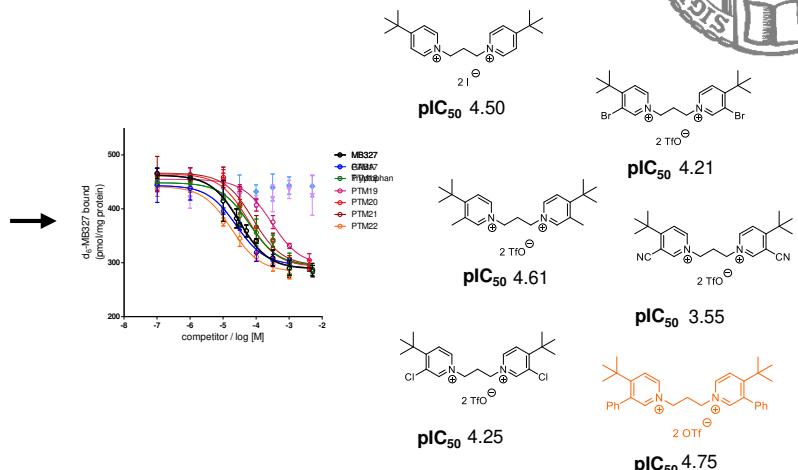
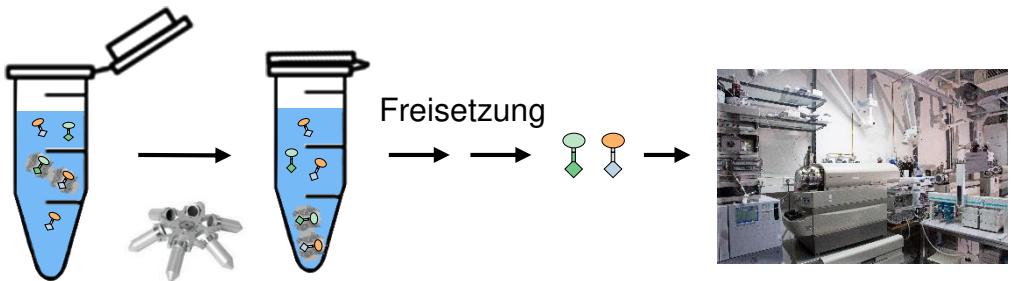


Biologische Charakterisierung
- funktionale Assays

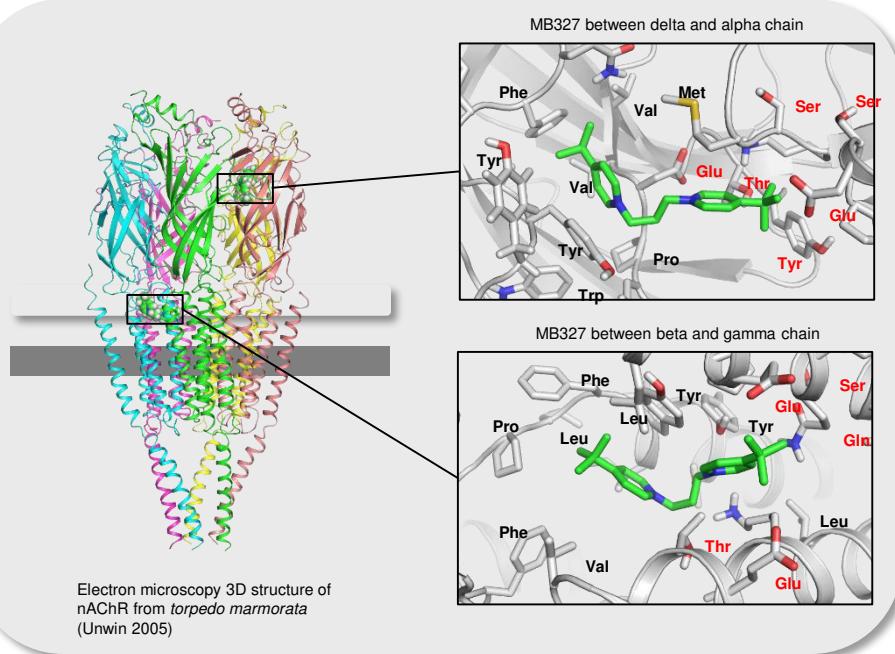


In Kooperation mit dem
Institut für Pharmakologie und Toxikologie der Bundeswehr

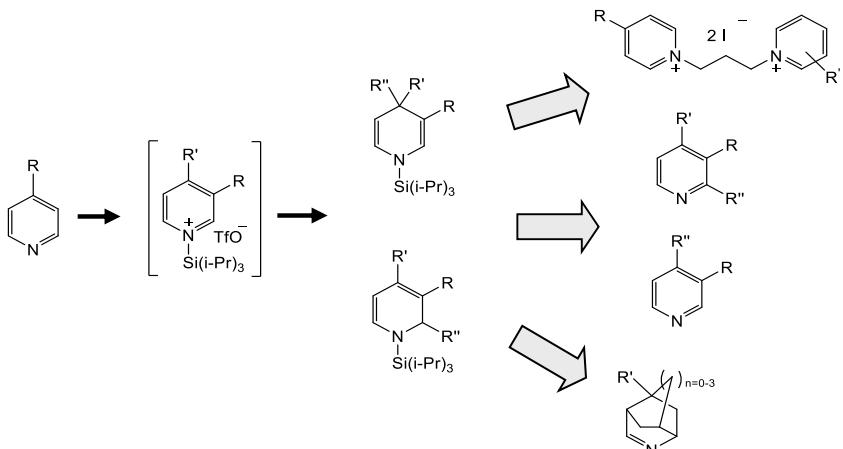
Resensitizer nikotinischer Acetylcholinrezeptoren



S. Sichler, G. Höfner, S. Rappenglück, T. Wein, K. V. Niessen, T. Seeger, F. Worek, H. Thiermann, F. F. Painterer, K. T. Wanner,
Development of MS Binding Assays targeting the binding site of MB327 at the nicotinic acetylcholine receptor, *Tox. Lett.*, in Press

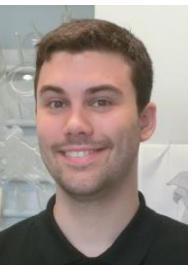


Bausatz für Synthesen von Pyridinderivaten



J. Bräckow, K. T. Wanner, "Direct Synthesis of 4,4-Disubstituted N-Silyl-1,4-Dihydropyridines", *Tetrahedron*, 2006, 62, 2395-2404.

Vielen Dank für Ihre Aufmerksamkeit!

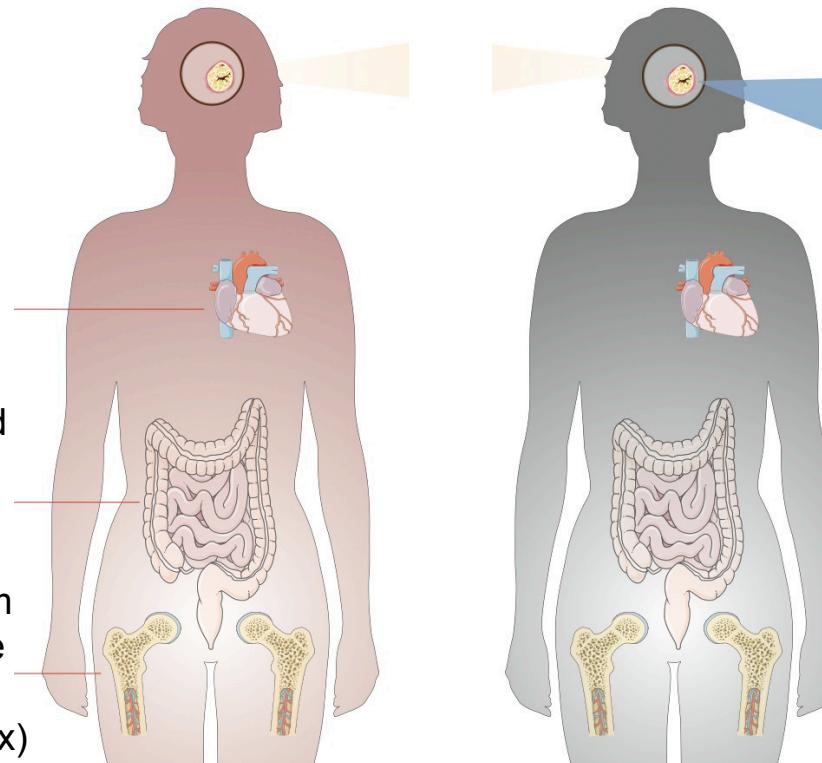




How to make Pharmaceutical Chemistry *smarter*?

The most potent anticancer drugs hit targets that are critical for cell survival - and therefore, which are needed in healthy as well as tumoural cells.

Major side-effects arise from *on-target interactions*, in the *wrong areas of the body* (here: cardio, GI, immunotox)



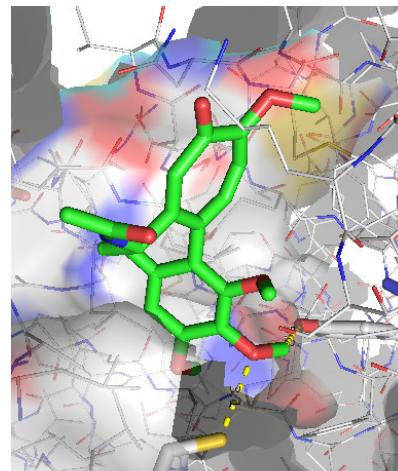
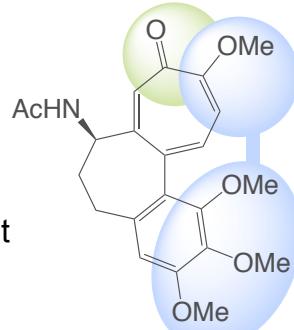
We redesign key drug features, so our derivatives remain inactive throughout an organism, *except* at a tissue we want to hit.

We often use photoswitching, enzymatic processing, or redox strategies to mask or reveal the bioactivity of our derivatives.

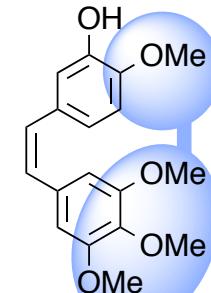
A case study: Targeting Antimitotics with Light



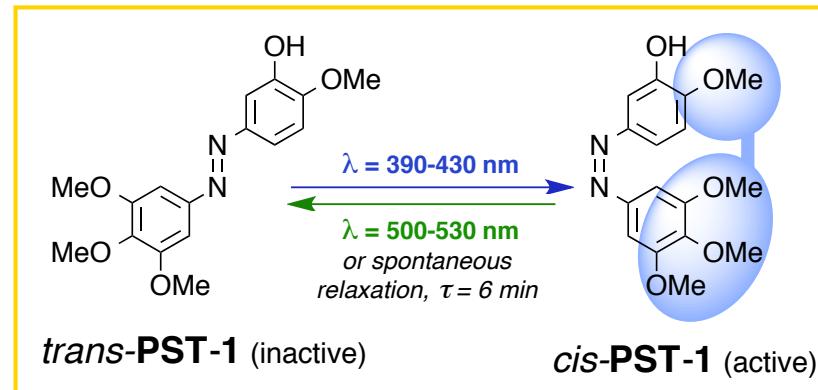
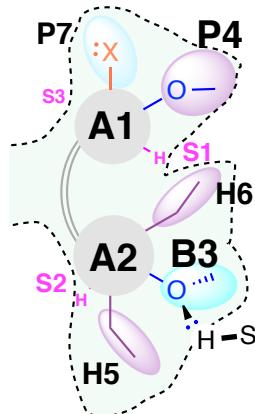
1. select and analyse potent antimitotic



2. study SAR



3. develop pharmacophore model

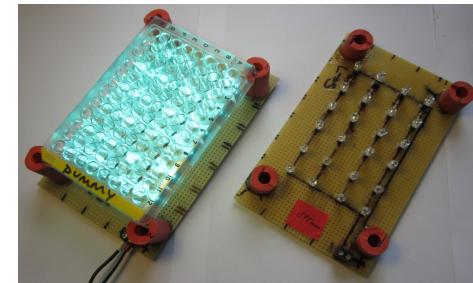
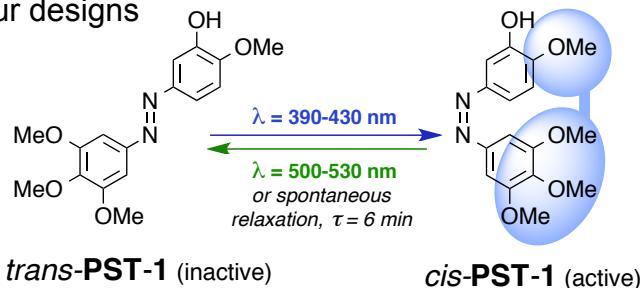


4. **our work:** design a switchable analogue, where one isomer [*cis*] fits the pharmacophore, the other [*trans*] does not.

A case study: Targeting Antimitotics with Light

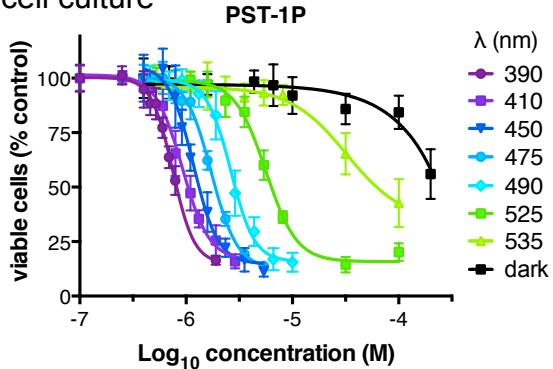


5. synthesise a small panel of our designs

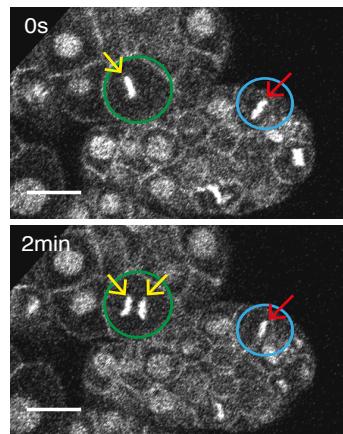


6. run biological assays with selective activation or activity suppression (here: by light)

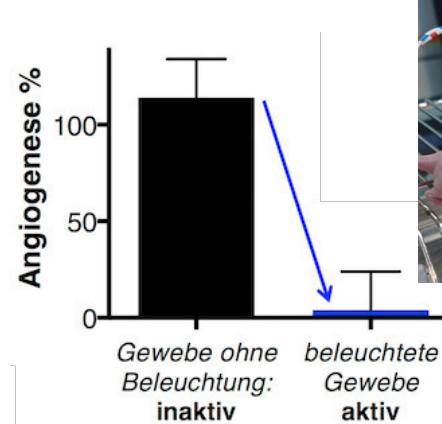
7. Study activity switching in cell culture



8a. Use as unique, high-precision tool to achieve new research possibilities



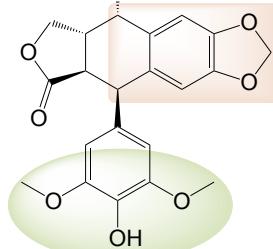
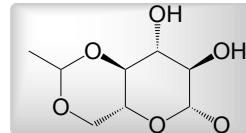
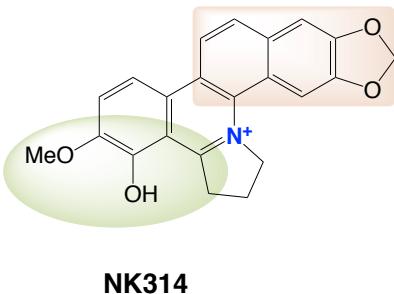
8b. Apply as switchable drug *in vivo* to target antimitotic/anticancer effects



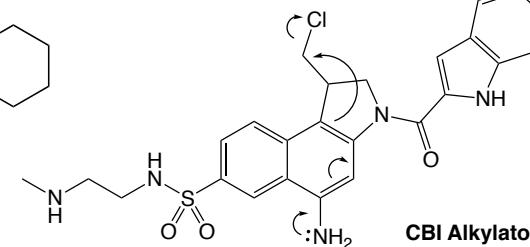
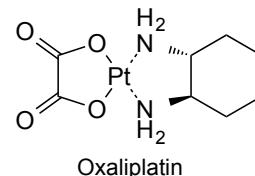
Other drug classes we work on



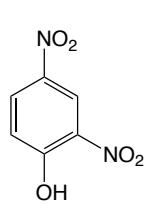
Topoisomerase Inhibitors: *photoswitching*



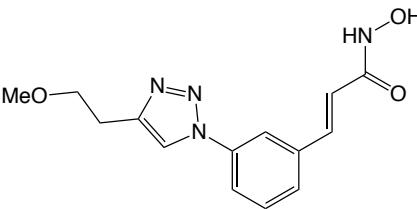
DNA Lesion Agents: *mechanisms to trigger bioactivity*



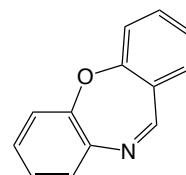
Other Targets



mitochondrial
depolariser:
activity switching



HDAC inhibitor:
mechanism elucidation



Inhibitors of TRP channels
(pain / heat / pH sensation):
binding site studies

Anticancer Strategies
Light & Light-Switching
Organic Synthesis
Redox in Biology

Targeting Pharmadude/tte/s

Thorn-Seshold Group
Pharmaceutical Chemistry



Join us! Thesis, F-Praktika, & PhD positions in pharmaceutical chemistry



Pharmakologie • Prof. Dr. Christian Wahl-Schott

Tag der Forschung

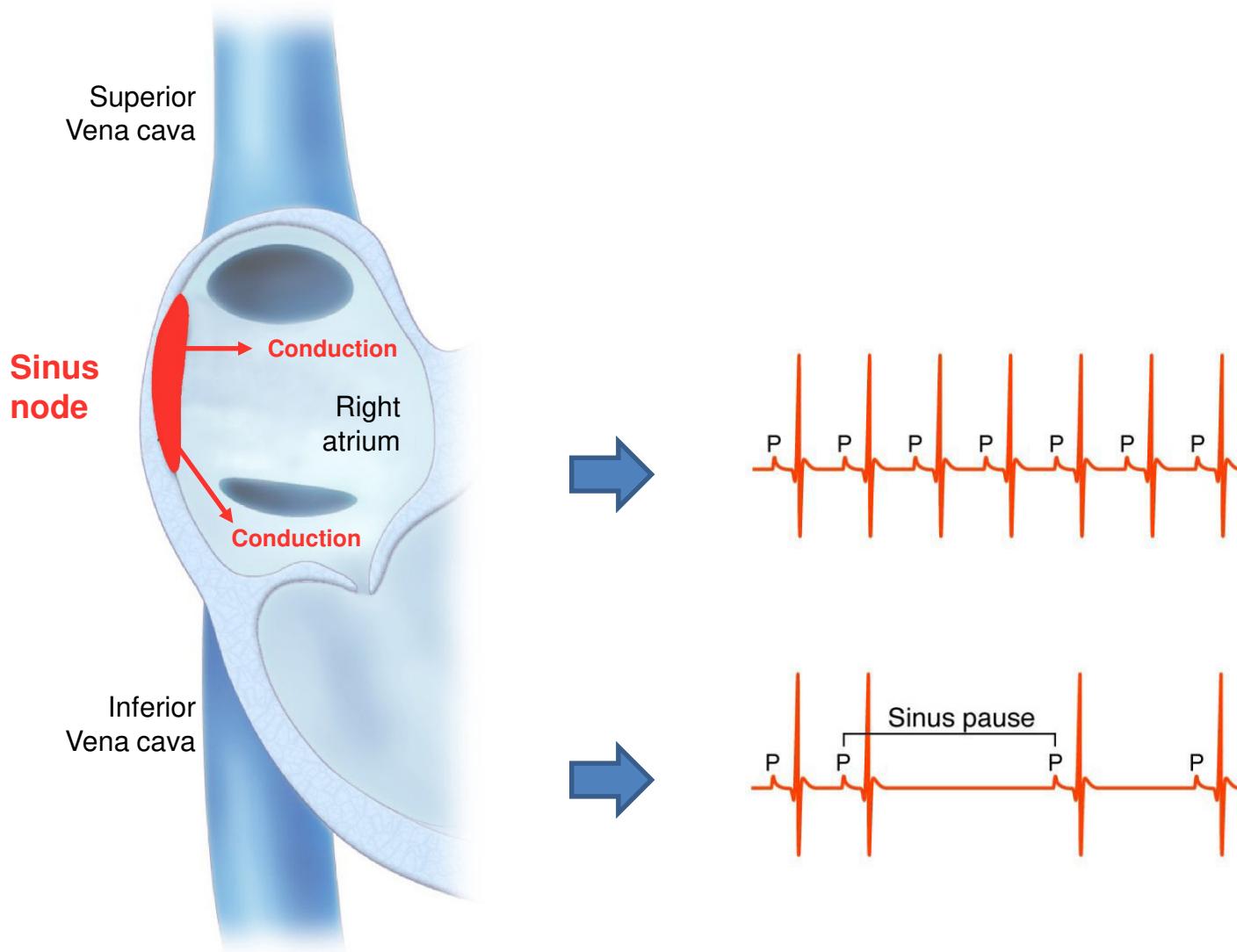
Cardiac pacemaking

Anatomy

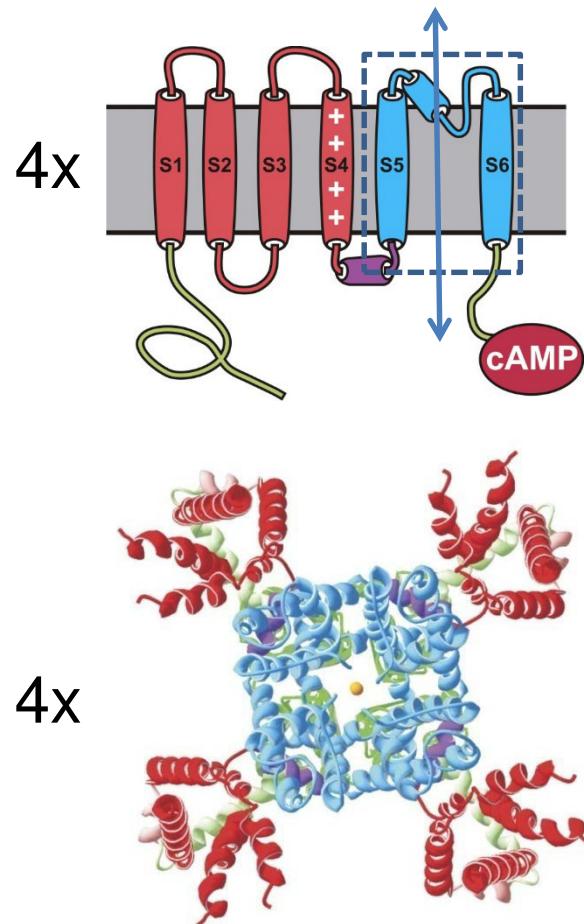
Clinical Pharmacy



Cardiac functions of pacemaker channels



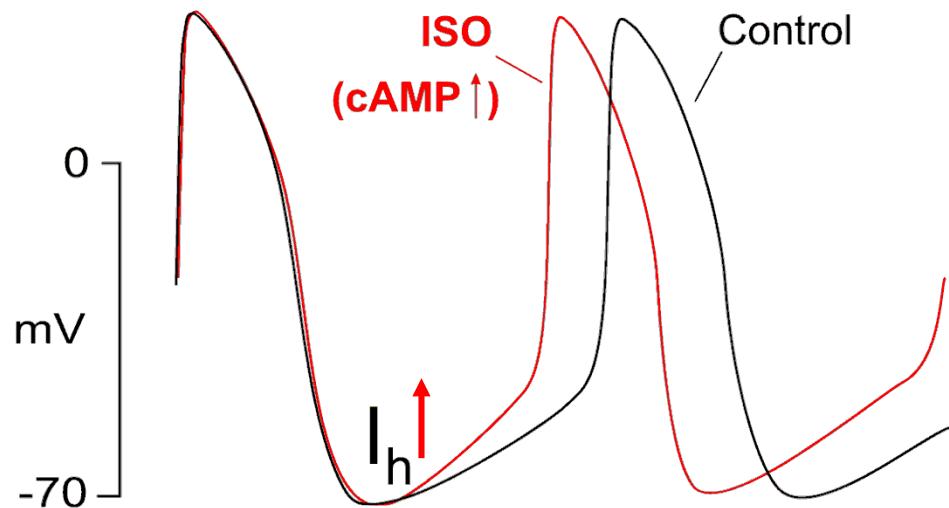
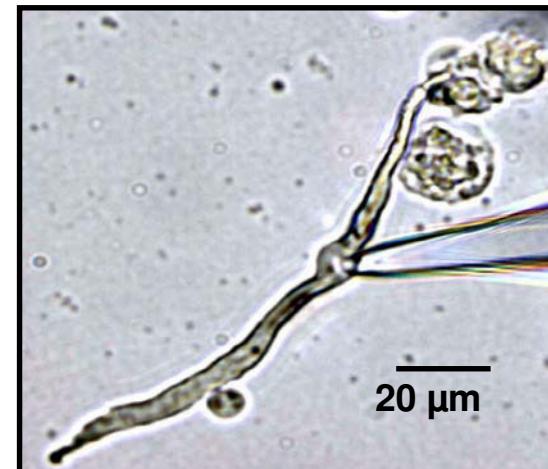
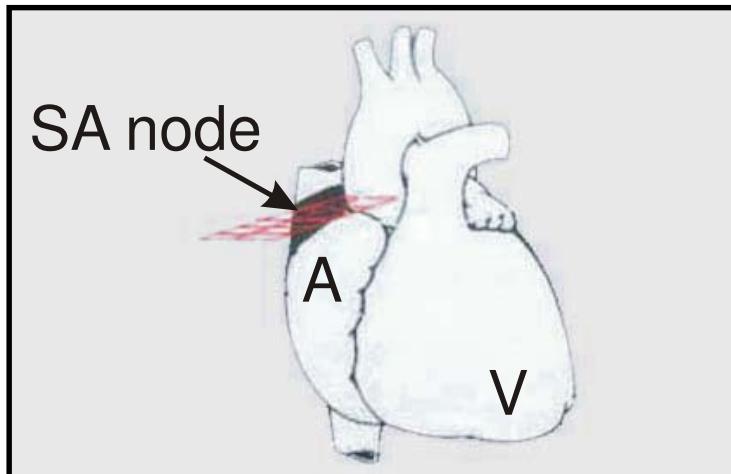
HCN pacemaker channels and genetic mouse models



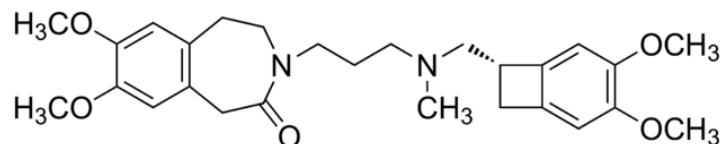
	cAMP	SAN
HCN2	+	+
HCN4	+	+
HCN1	-	+
HCN3	-	-

From the MacKinnon Laboratory

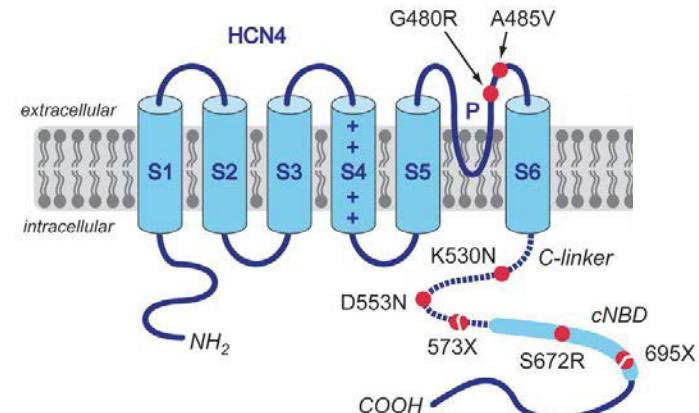
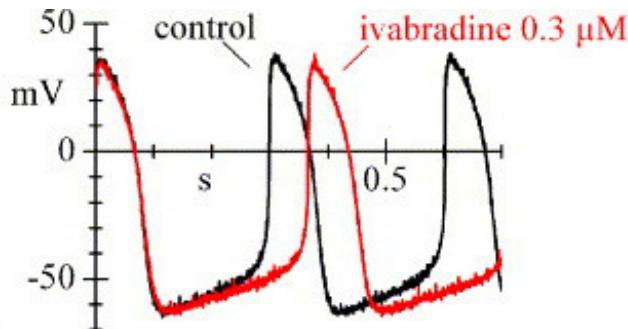
Role of I_h/I_f in the generation of cardiac pacemaker potentials



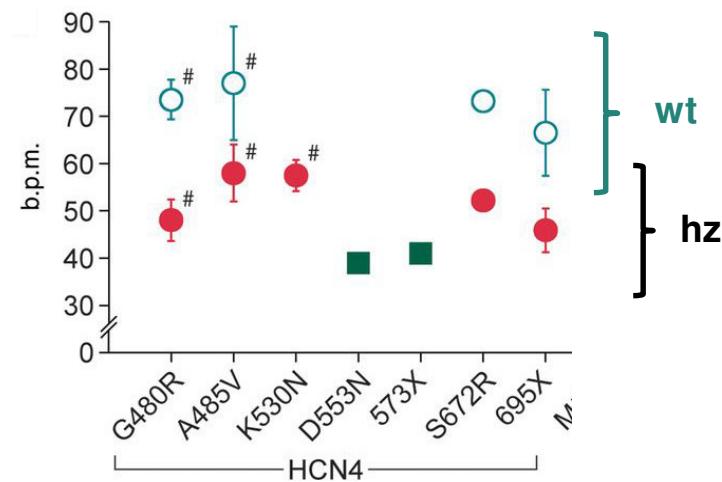
Key role of HCN4 in sinoatrial pacemaking



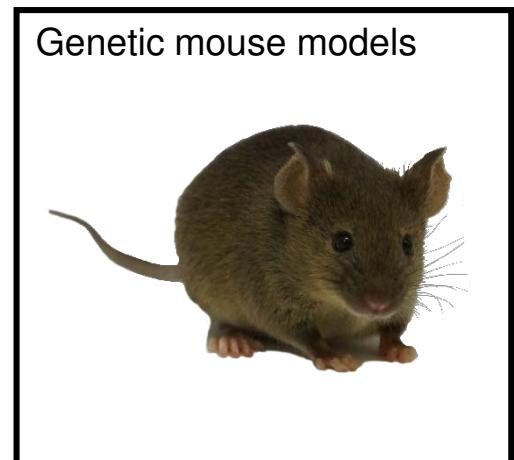
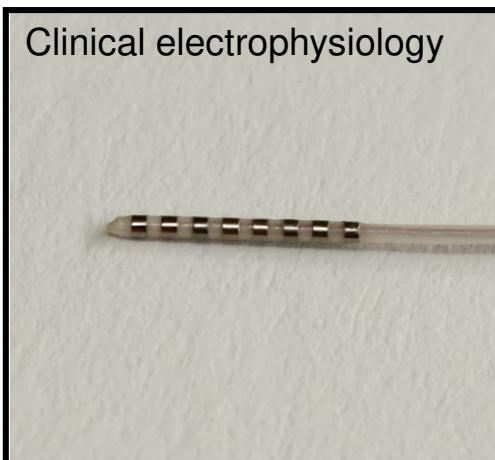
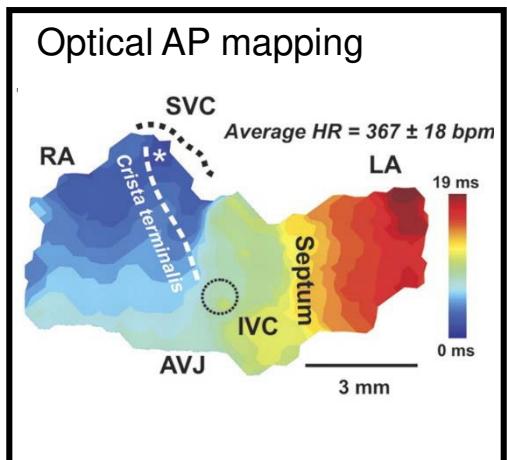
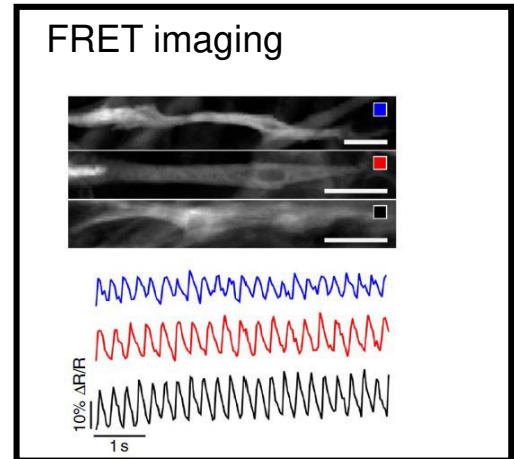
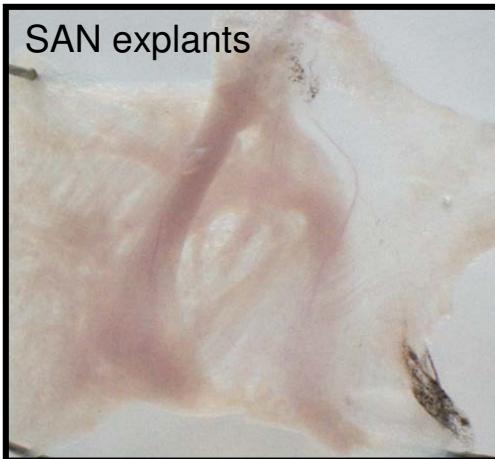
Ivabradine (Procotalan®)



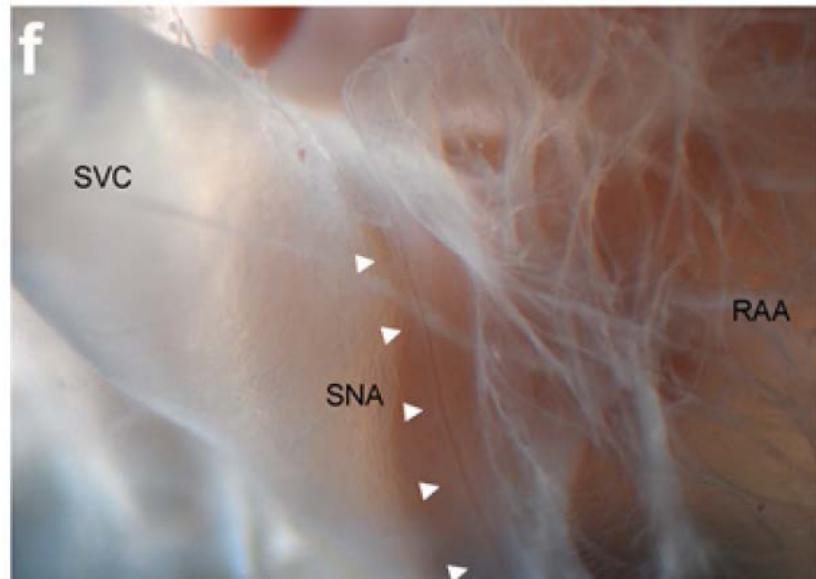
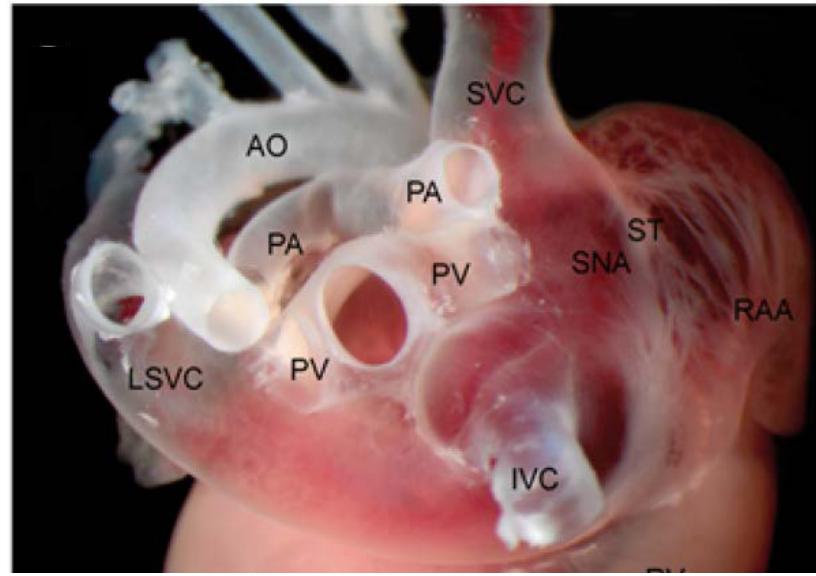
Resting heart rate



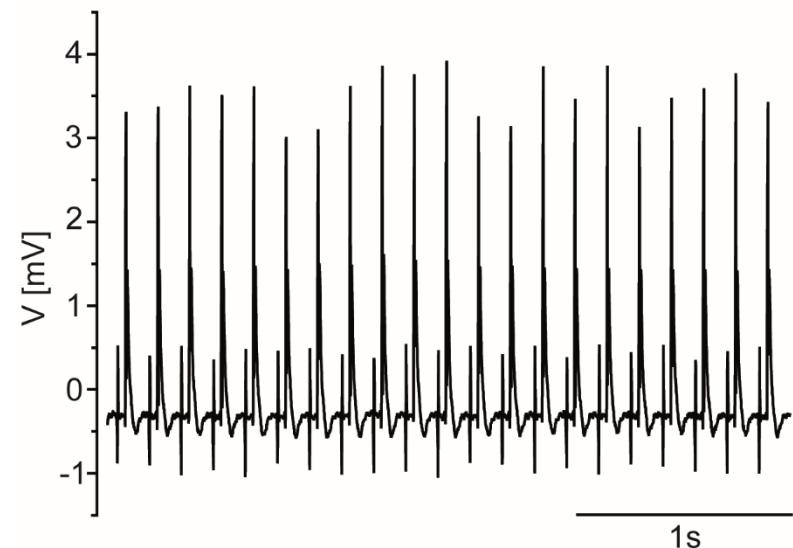
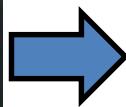
Experimental approaches to characterize pacemaking



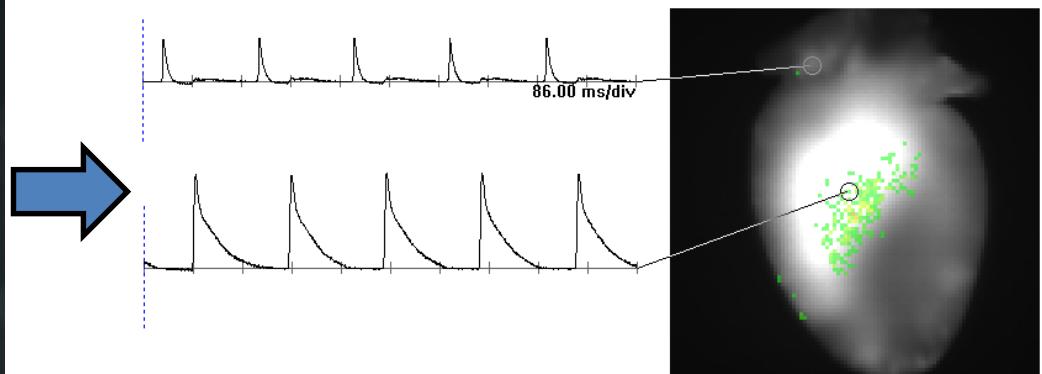
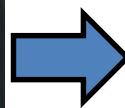
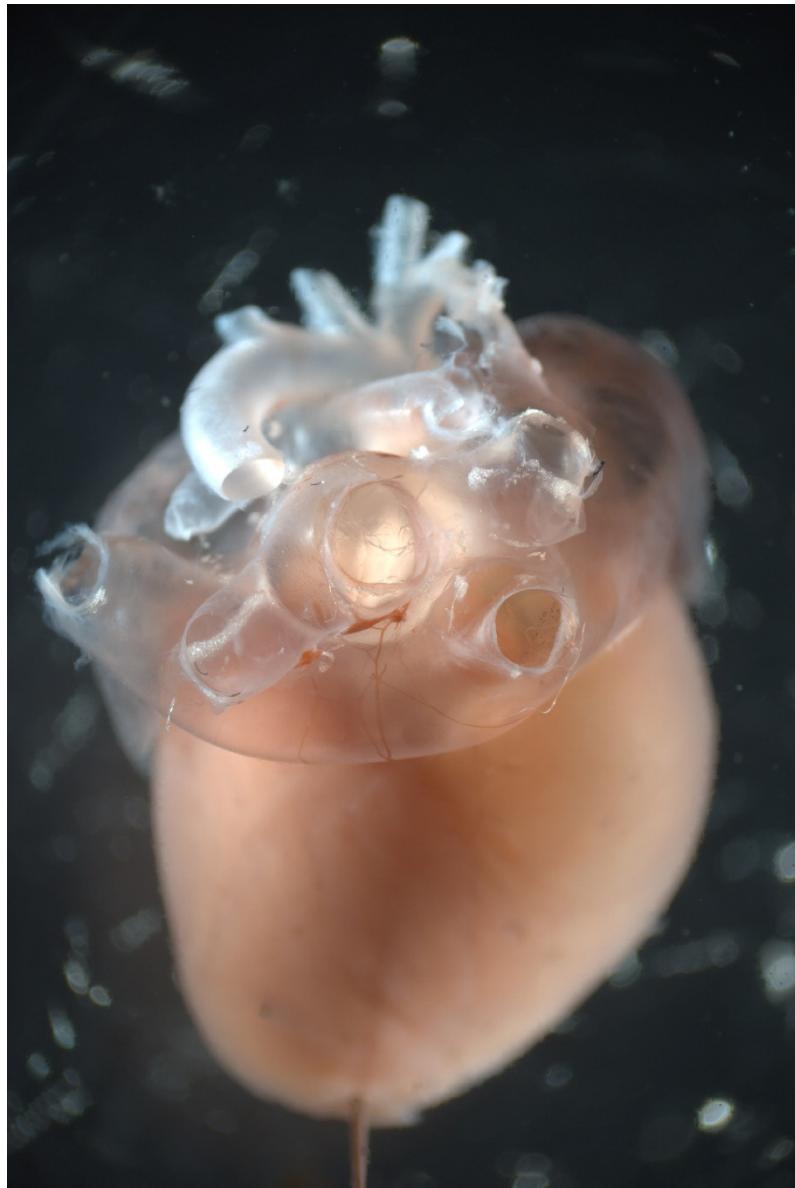
Anatomical studies of sinoatrial node



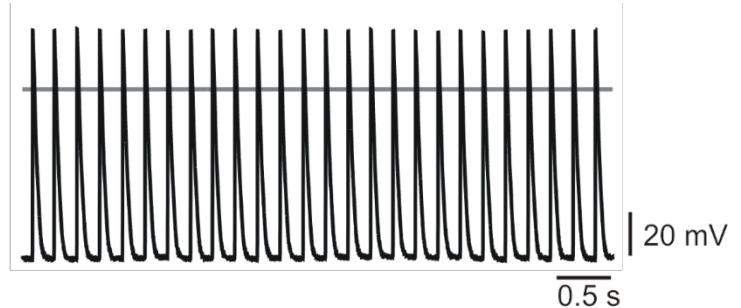
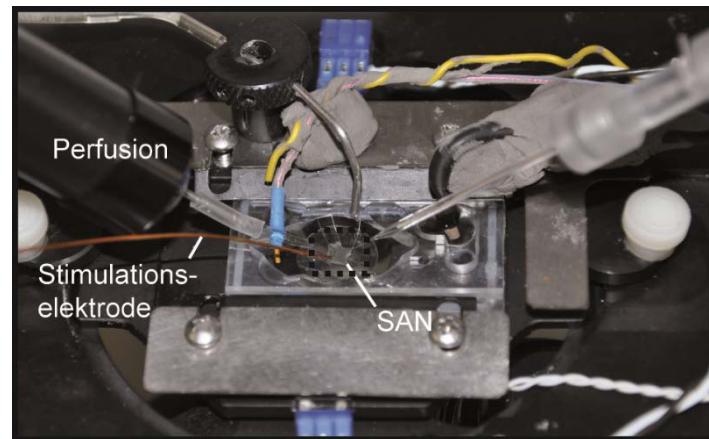
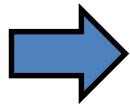
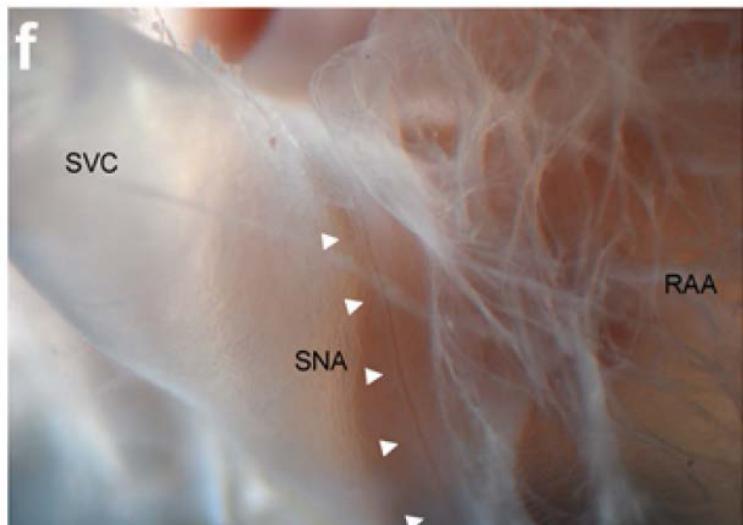
Experimental approaches to characterize pacemaking



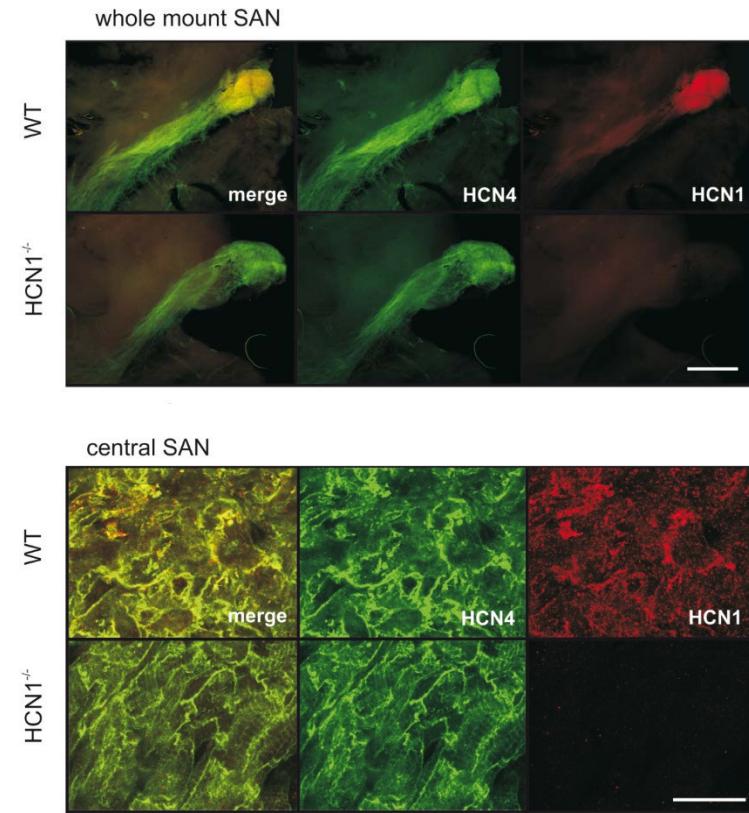
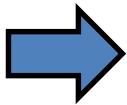
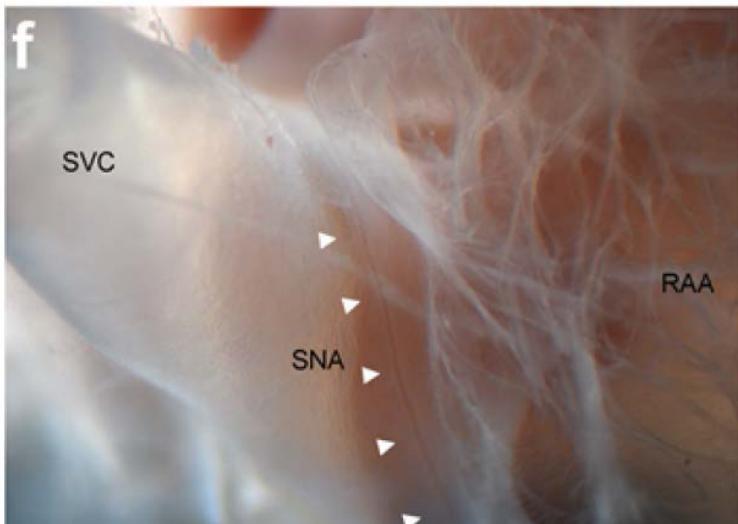
Experimental approaches to characterize pacemaking



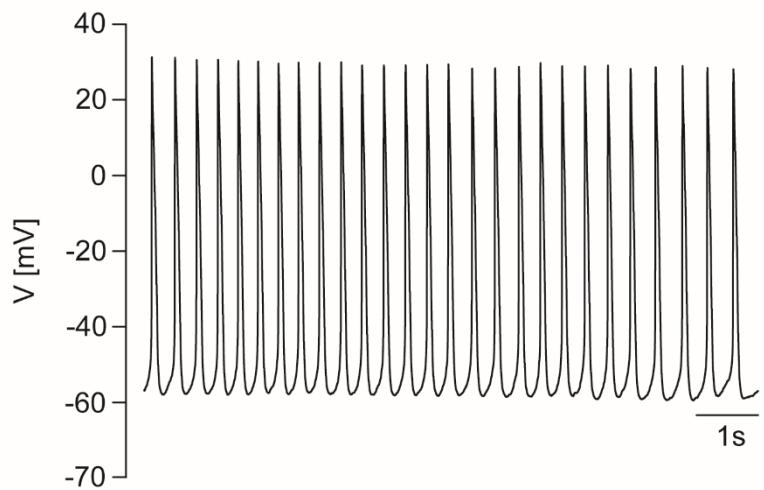
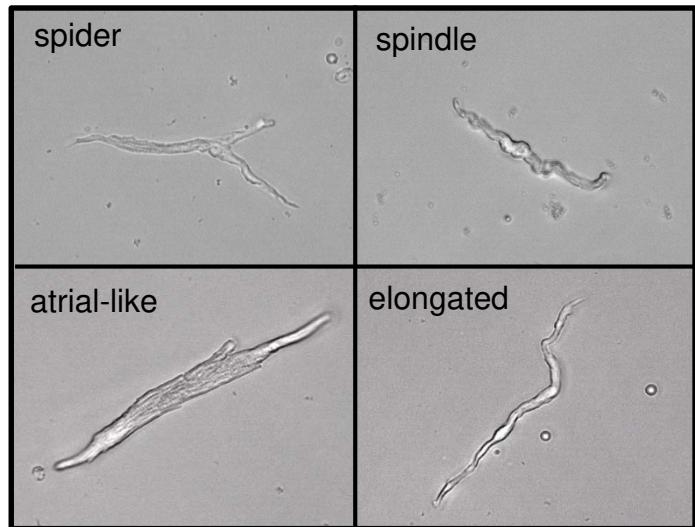
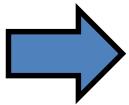
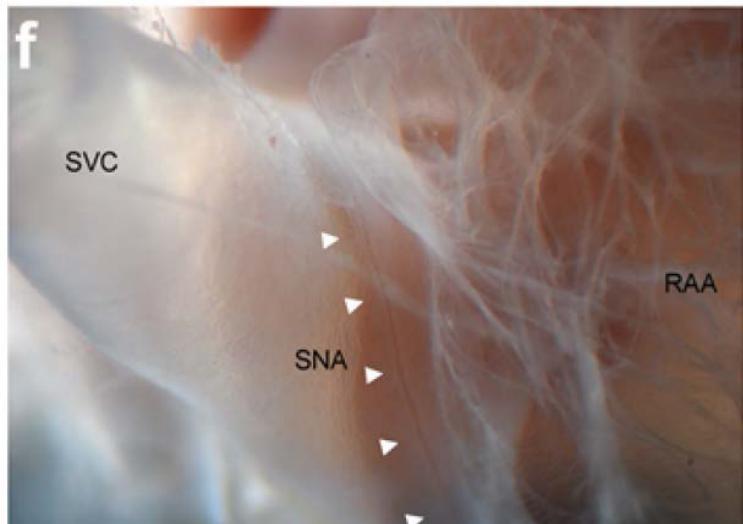
Experimental approaches to characterize pacemaking



Experimental approaches to characterize pacemaking



Dissociation of sinoatrial node cells



Pharmakologie • Prof. Dr. Christian Wahl-Schott

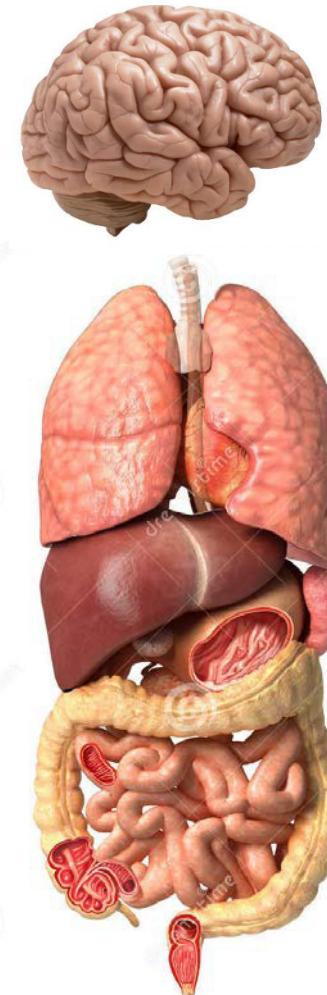
Tag der Forschung

Cardiac pacemaking

Anatomy

Clinical Pharmacy









GEMEINSAM AM KRANKENBETT

Was künftige Ärzte und Apotheker im Studium voneinander lernen – und wie die Patienten profitieren

Dass Ärzte und Apotheker im klinischen Alltag eng zusammen arbeiten, ist in vielen Ländern selbstverständlich, in Deutschland aber eher selten. Dabei liegen die Vorteile auf der Hand und sind wissenschaftlich untermauert: mehr Sicherheit für den Patienten durch passgenaue Medikamente und Dosierung, durch Vermeiden gefährlicher Wechselwirkungen, durch Optimierung der Behandlung. Um hier international aufzuschließen, wurde am Department Pharmazie und an der Medizinischen Fakultät der LMU das innovative Großprojekt POP Art (siehe Kasten) gestartet – in dieser Form bisher einmalig in Deutschland.



Illustration: Caroline Strenkert

Apothekerin Dr. Yvonne Hopf ist

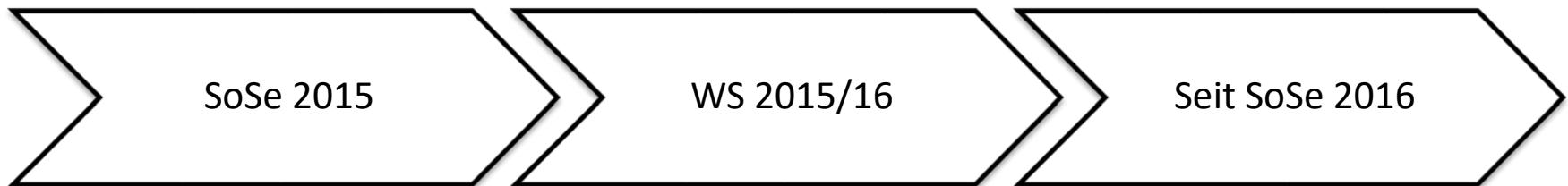
weiter auszubauen. Um das erfolgreich umzusetzen, ist das Projekt eng mit der Pharmakologie für Naturwissenschaften

nisse sollen zeitnah ins jeweilige Curriculum eingebaut werden.

Dr. Yvonne Hopf: „Das Lernen von Studierenden unterschiedlicher Fachrichtungen in einer gemeinsamen Gruppe gilt im Gesundheitswesen als Voraussetzung für optimierte Patientenversorgung. Es verbessert die spätere berufliche Zusammenarbeit, fördert Verständnis und Respekt zwischen den unterschiedlichen Berufen. Die bisherigen Ergebnisse waren durchweg positiv. Den Pharmaziestudierenden gefielen besonders die Einblicke in den Klinikalltag, die Zusammenarbeit ohne Vorurteile, den Unterschied in der Herangehensweise an einen Patienten zu sehen, also den zwischen der Erfassung



POP ART Übersicht



- **Pilotstudie**
- 15 Teilnehmer
- **SPICE 2D**
- **Qualitative Auswertung**
- **1. Kohorte**
- 68 Teilnehmer
- SPICE 2D
- Qualitative Auswertung
- **Neu: SOAP Analyse**
- **2. Kohorte**
- Teilnehmer
- SPICE 2D
- Qualitative Auswertung
- SOAP Analyse
- **Neu (Geplant):**
- **Durchführungs-empfehlung**
- **Shadowing Tool**
- **Format SOAP Analyse**







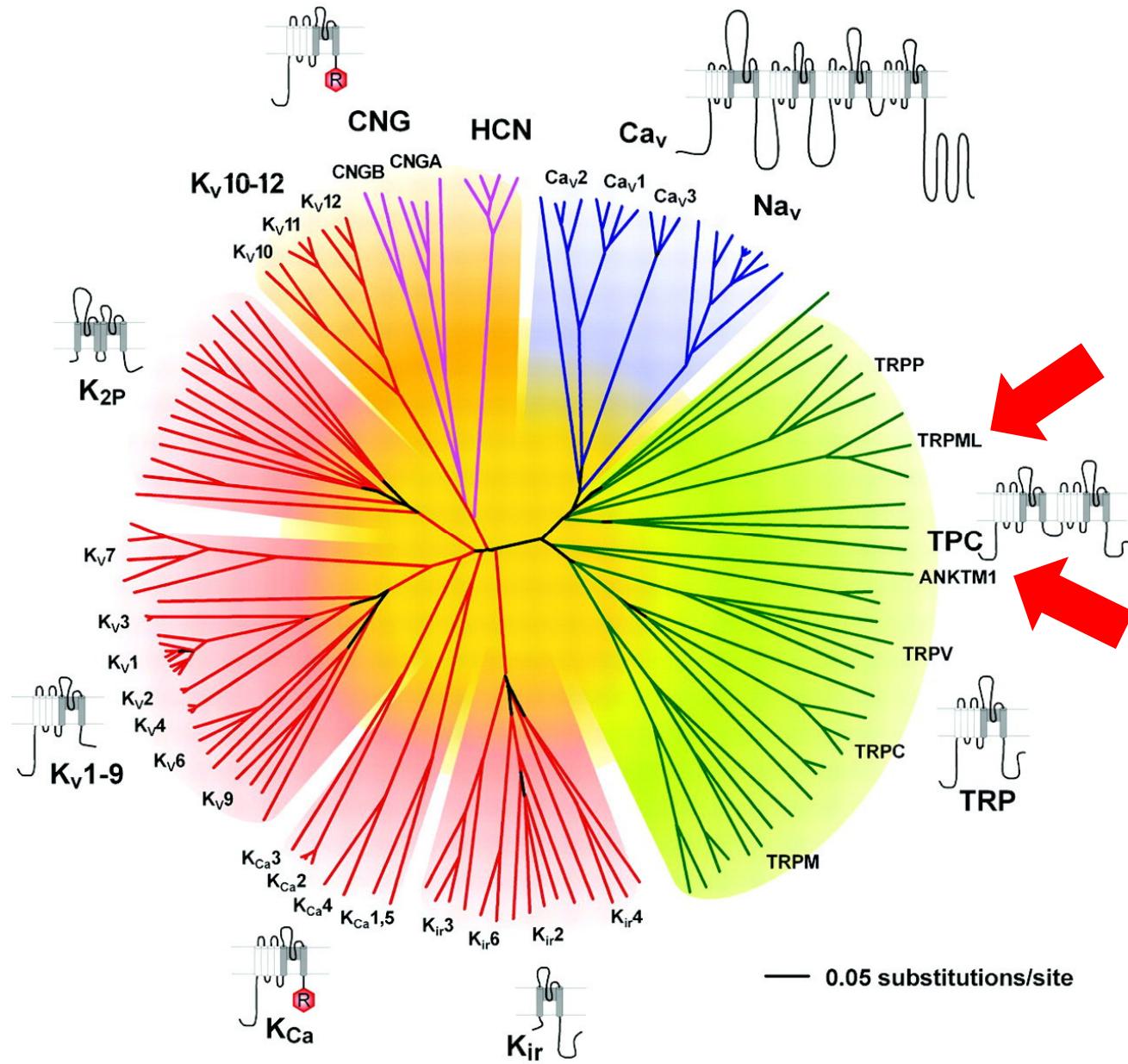
Insights into function and pharmacology of endolysosomal TRP channels

Christian Grimm

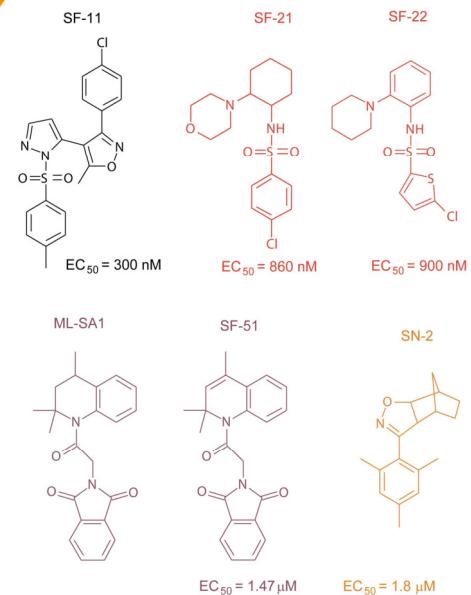
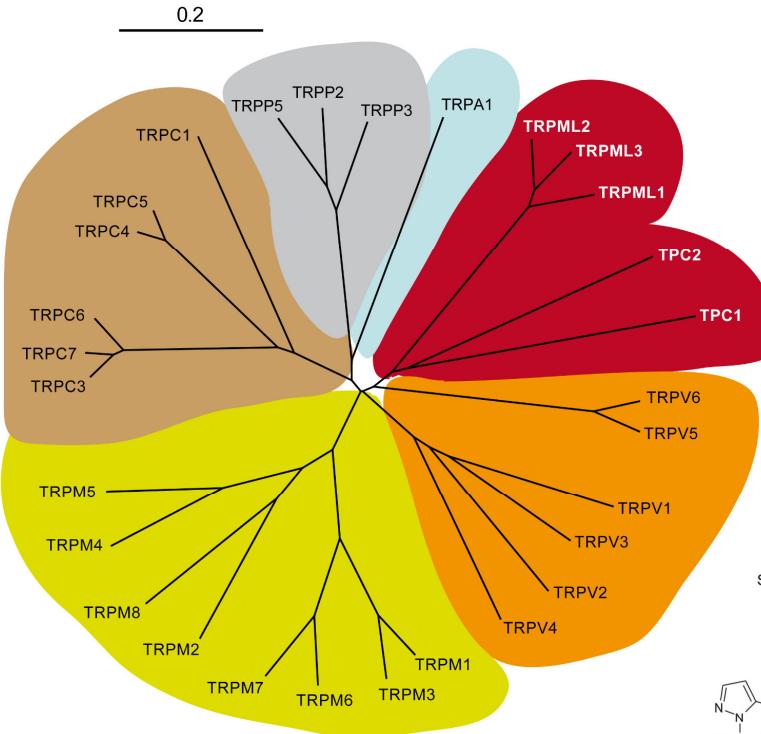
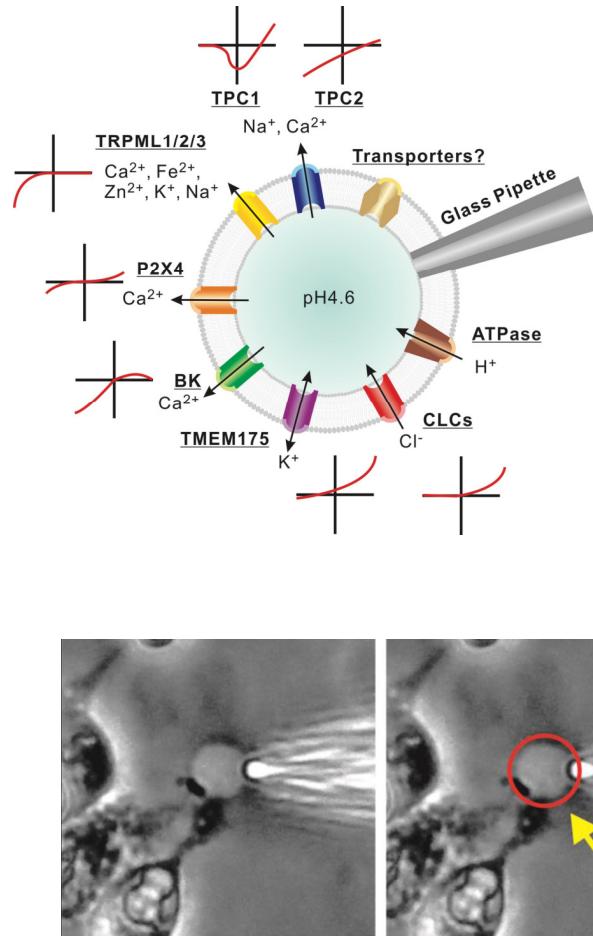
Department of Pharmacy/Pharmacology
LMU München

Lecture
Tag der Forschung LMU
Dec 1st 2017

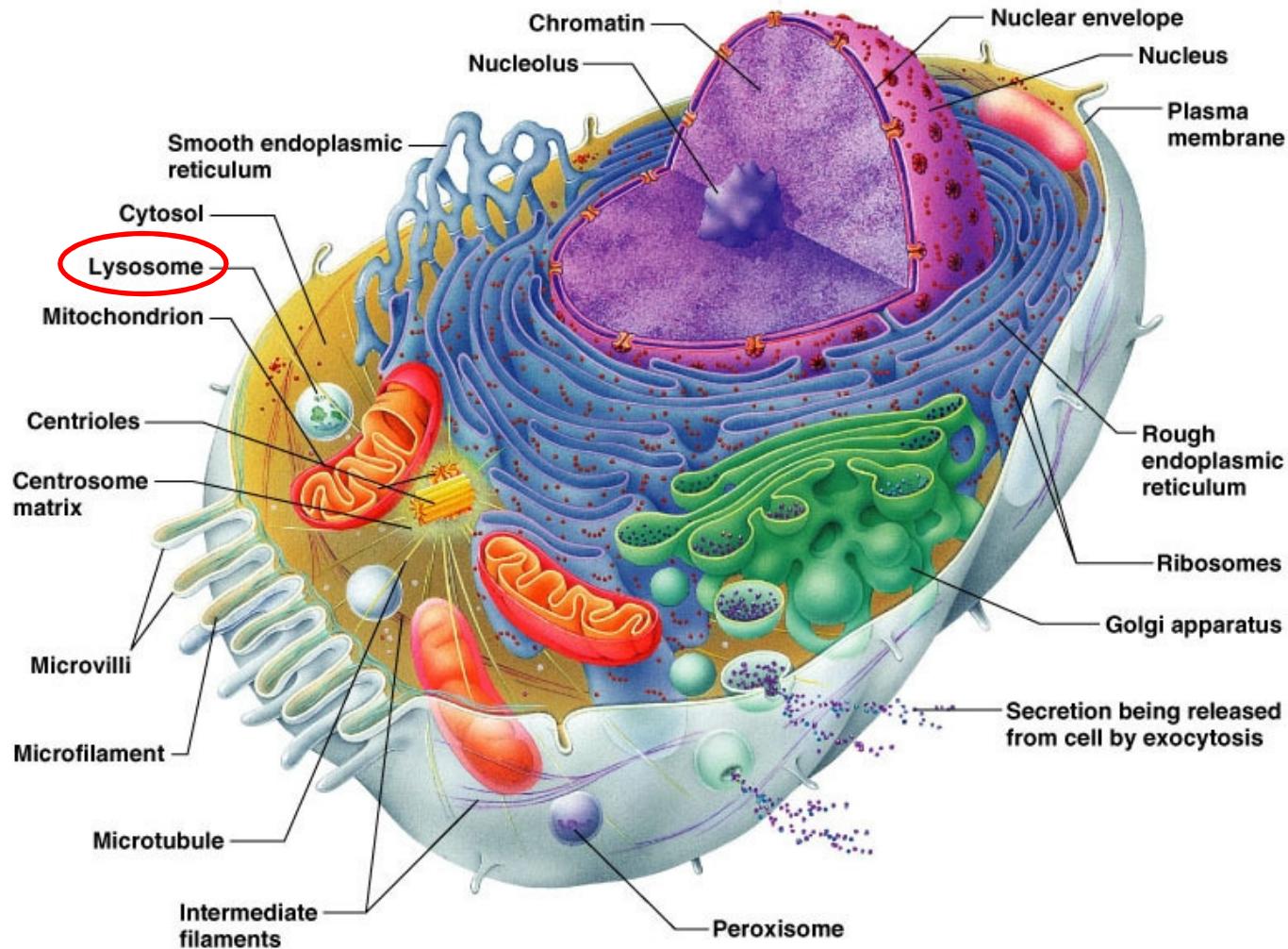
Ion channel research in the Dept. of Pharmacology



Endolysosomal ion channels



Endosomes and lysosomes are very small organelles

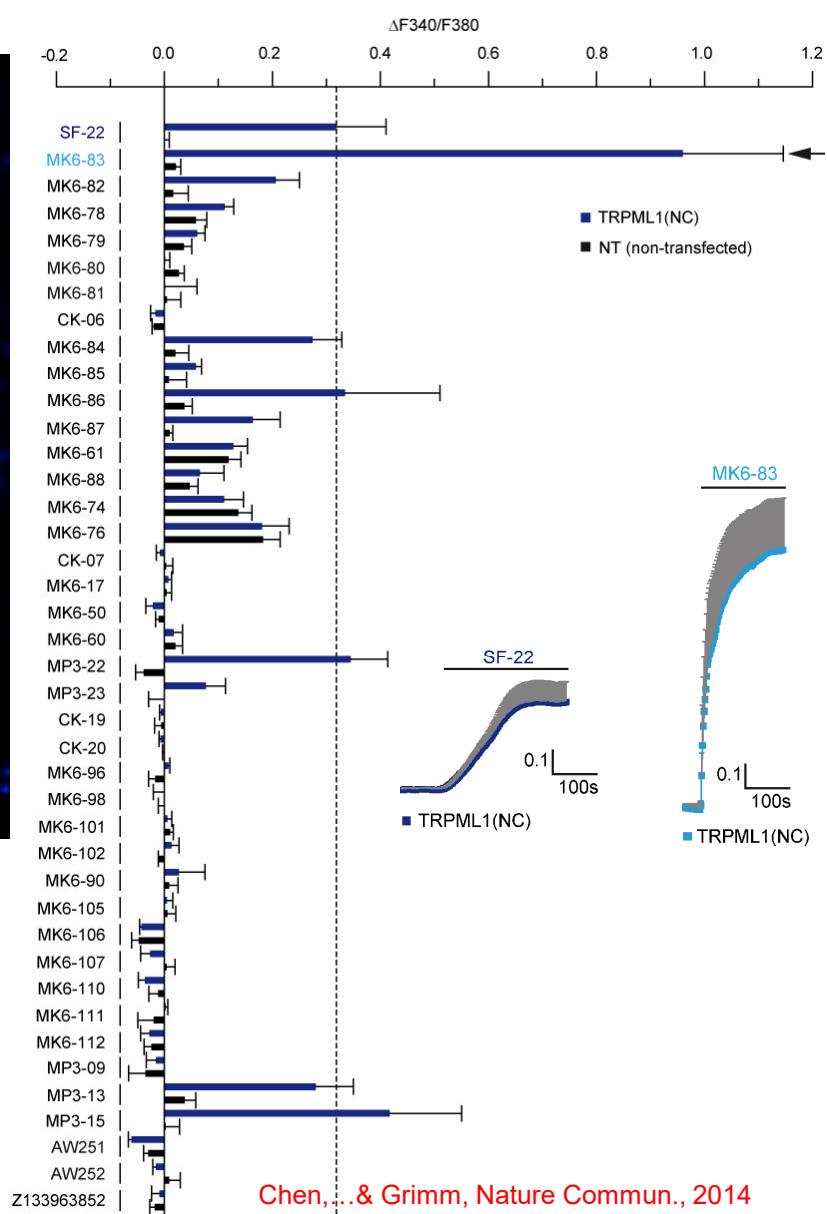
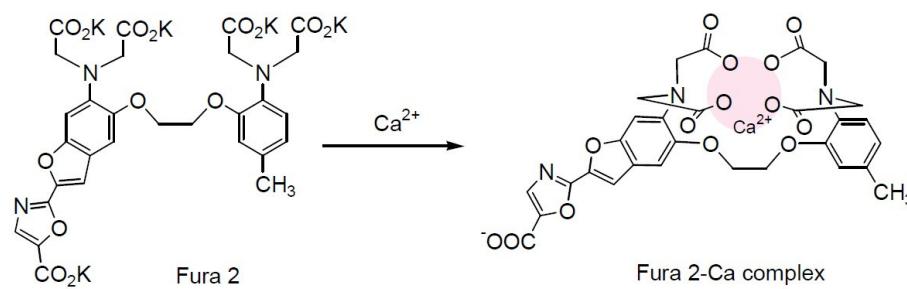
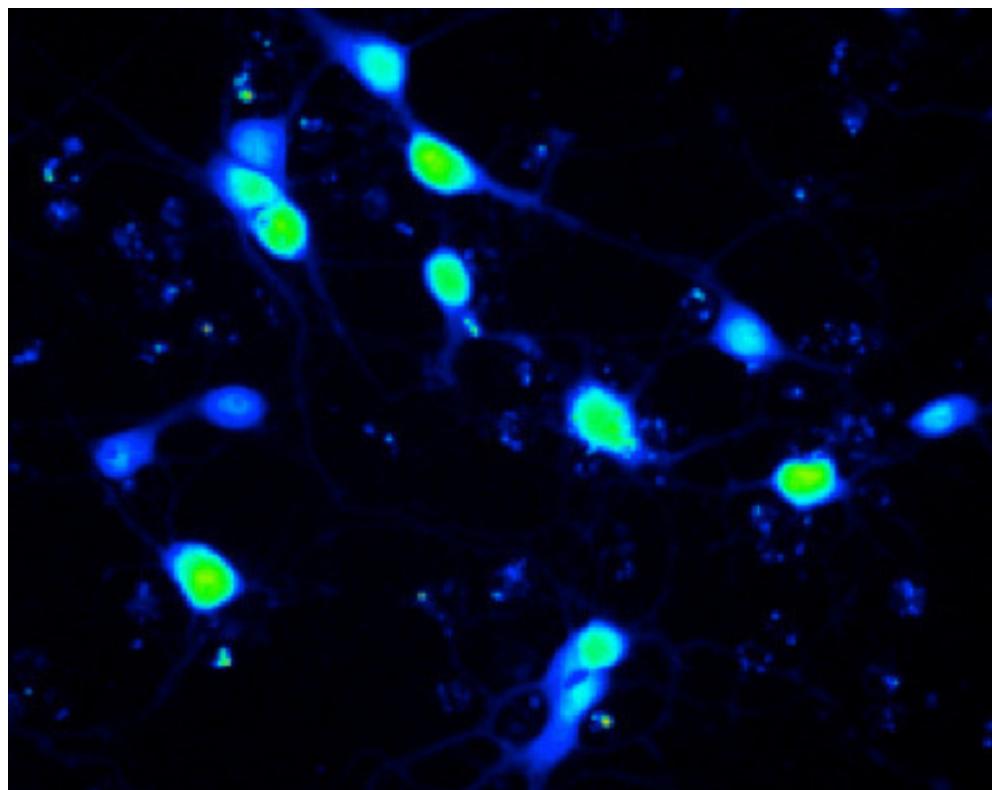


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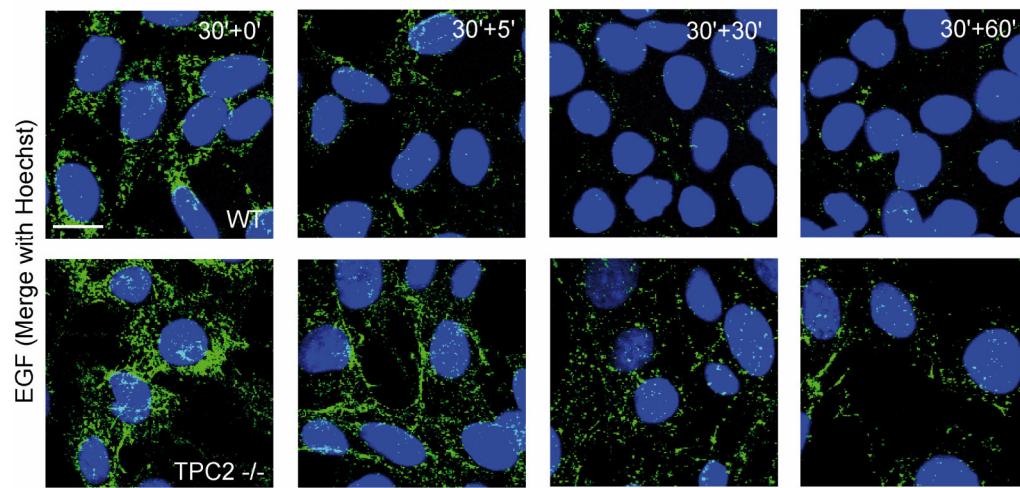
Methods

- 1) Calcium imaging (e.g. characterization of small molecule activators/inhibitors)
- 2) Confocal imaging (endolysosomal trafficking experiments)
- 3) Mouse genetics (KO mouse models, disease models)
- 4) Endolysosomal patch clamp (to investigate channels in their native context/EL membrane)
- 5) Standard molecular biology techniques (FRET, Western blot, cloning, qRT-PCR)

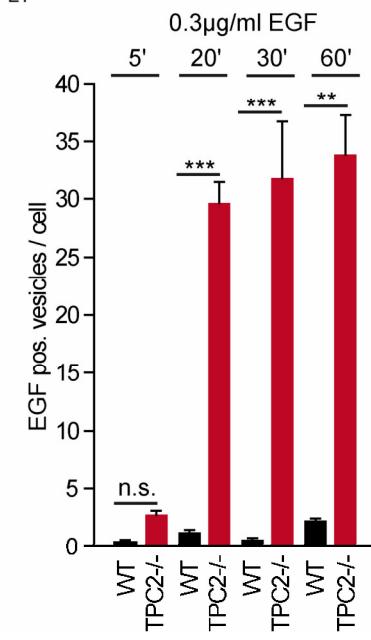
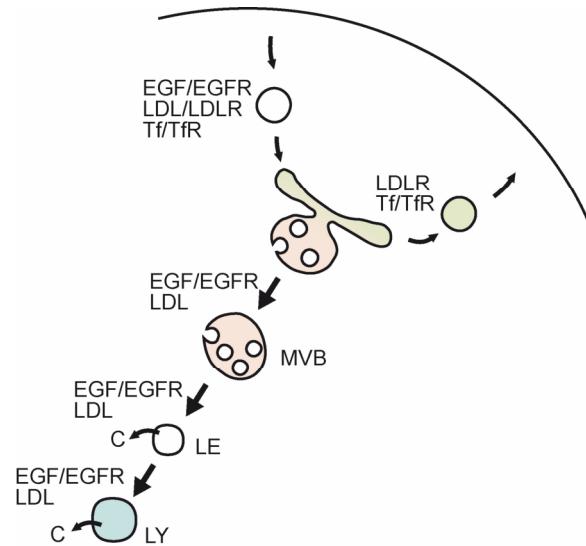
Methods – Calcium imaging



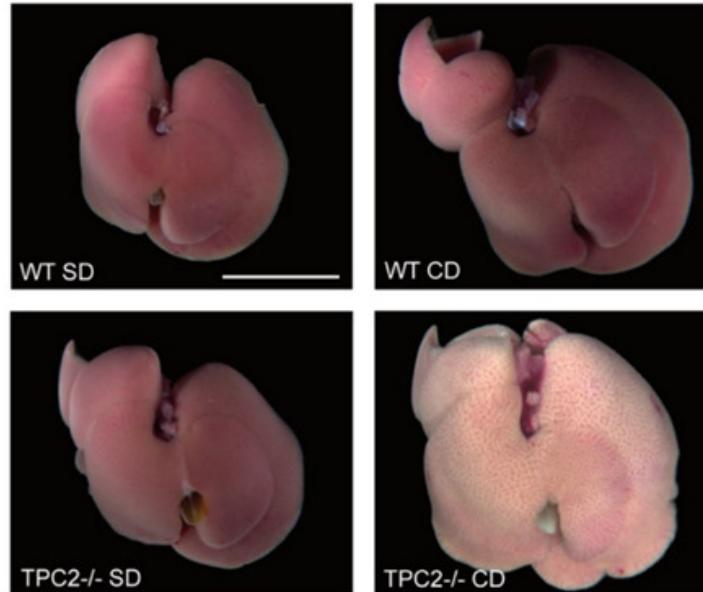
Methods – Confocal microscopy



Grimm et al., Nature Commun., 2014

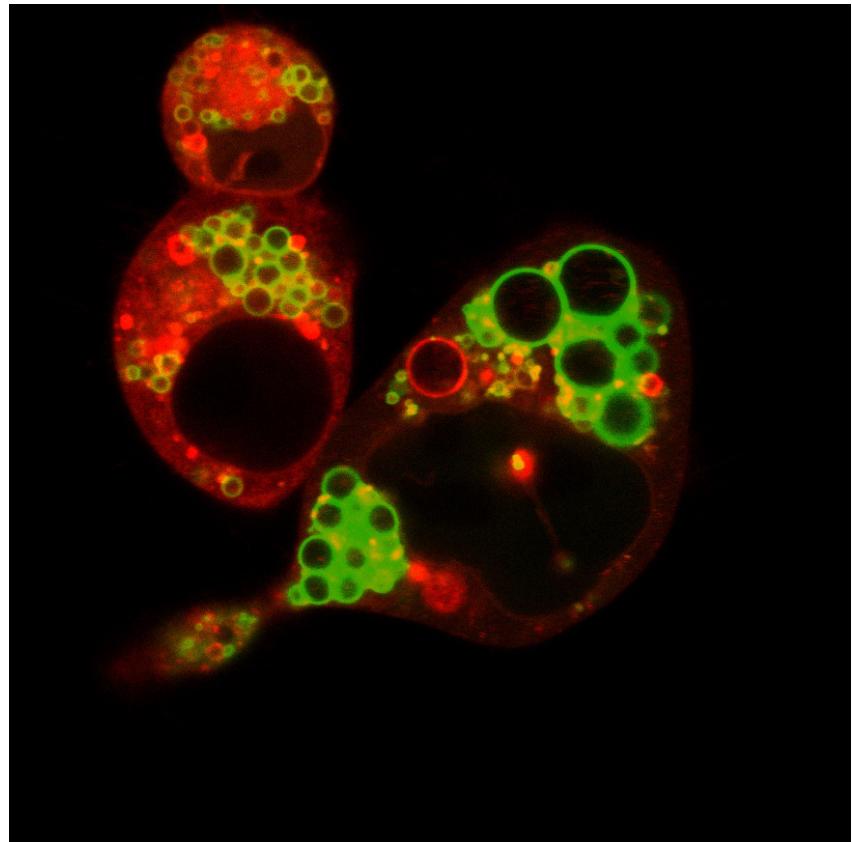


Methods – Mouse genetics

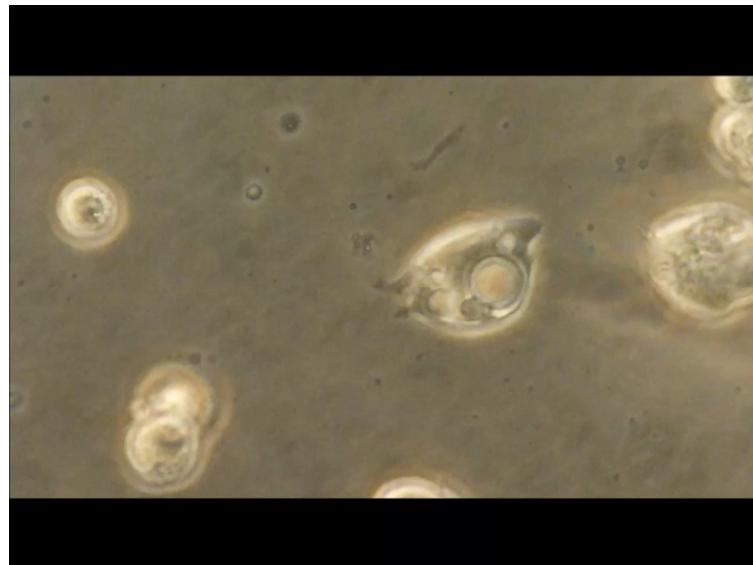


Grimm et al., Nature Commun., 2014

Methods – endolysosomal patch clamping

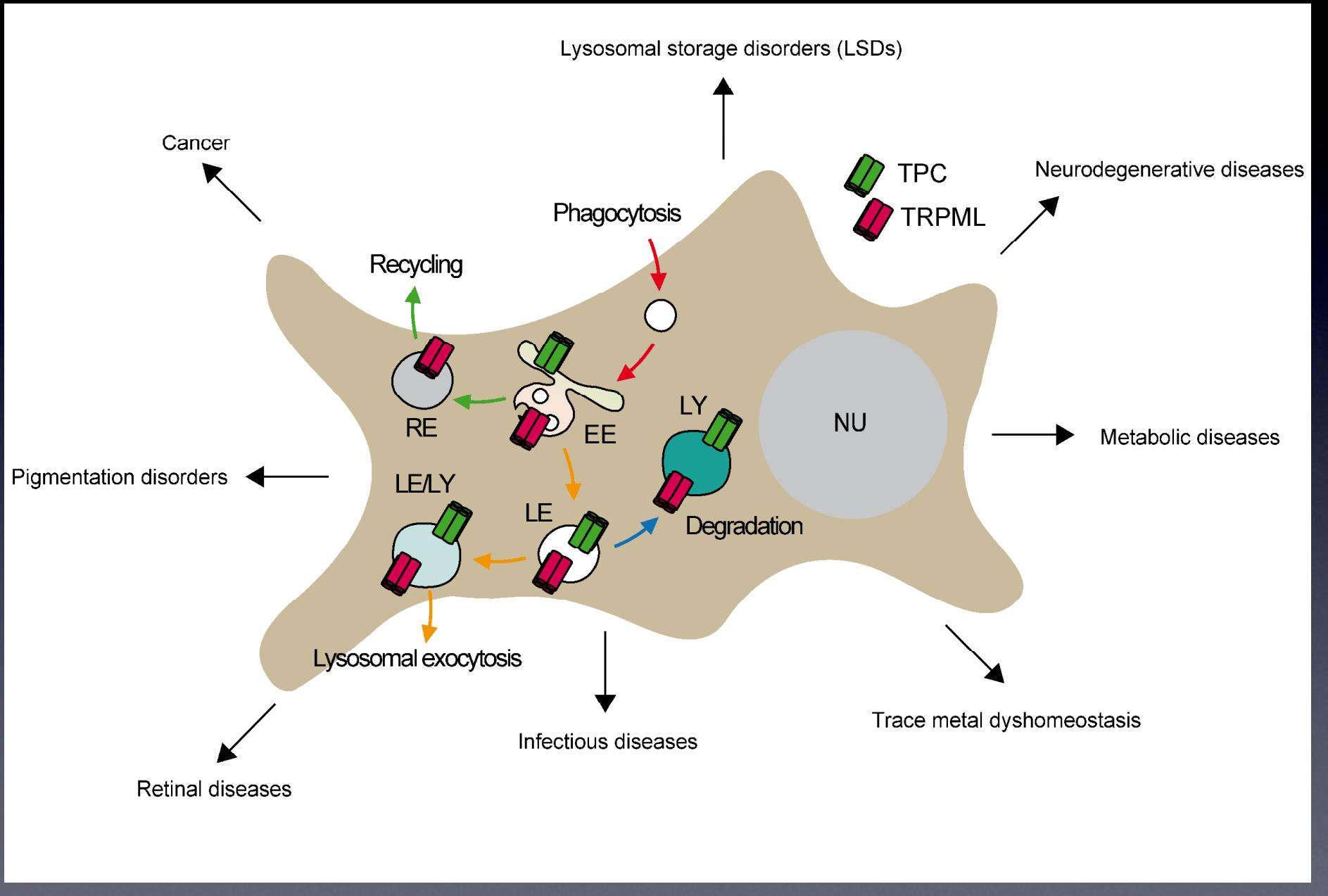


Chen et al., Cell Chem. Biol., 2017



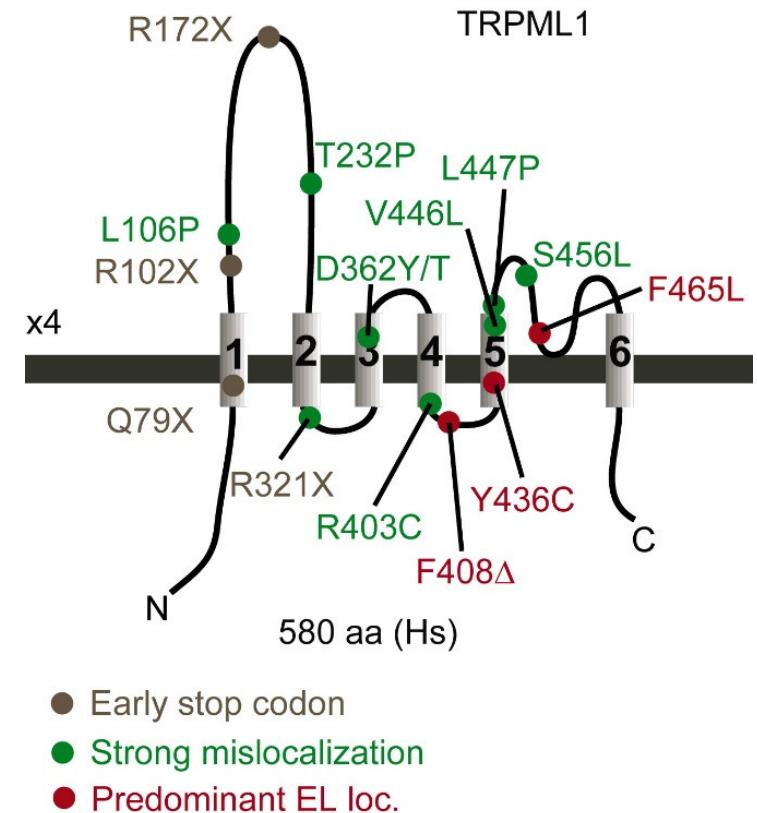
Chen et al., Nature Protoc., 2017

Disease relevance of endolysosomal cation channels



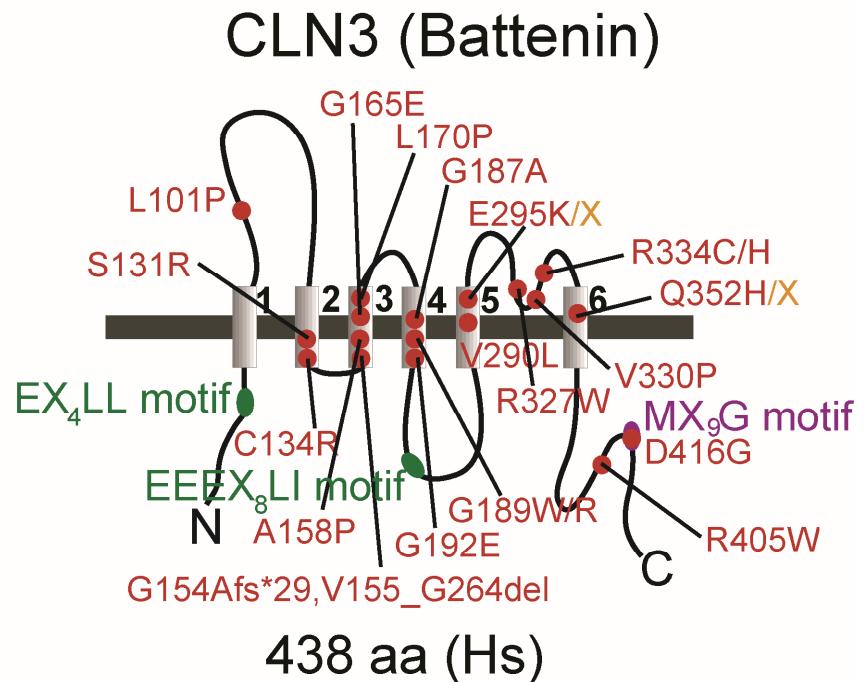
Lysosomal storage disorders

MLIV



Lysosomal storage disorders

NCL





Vorstellung AK Frieß

Tag der Forschung

LMU Muenchen
Department Pharmazie
Pharmazeutische Technologie und Biopharmazie

Top 10 Drugs 2016

#1 Adalimumab - Humira® (16 Mrd€)

2 Ledipasvir+Sofosbuvir - Harvoni® (9 Mrd€)

3 Etanercept - Enbrel® (8.9 Mrd€)

4 Rituximab - Rituxan® (8.6 Mrd€)

5 Remicade - Infliximab® (7.8 Mrd€)

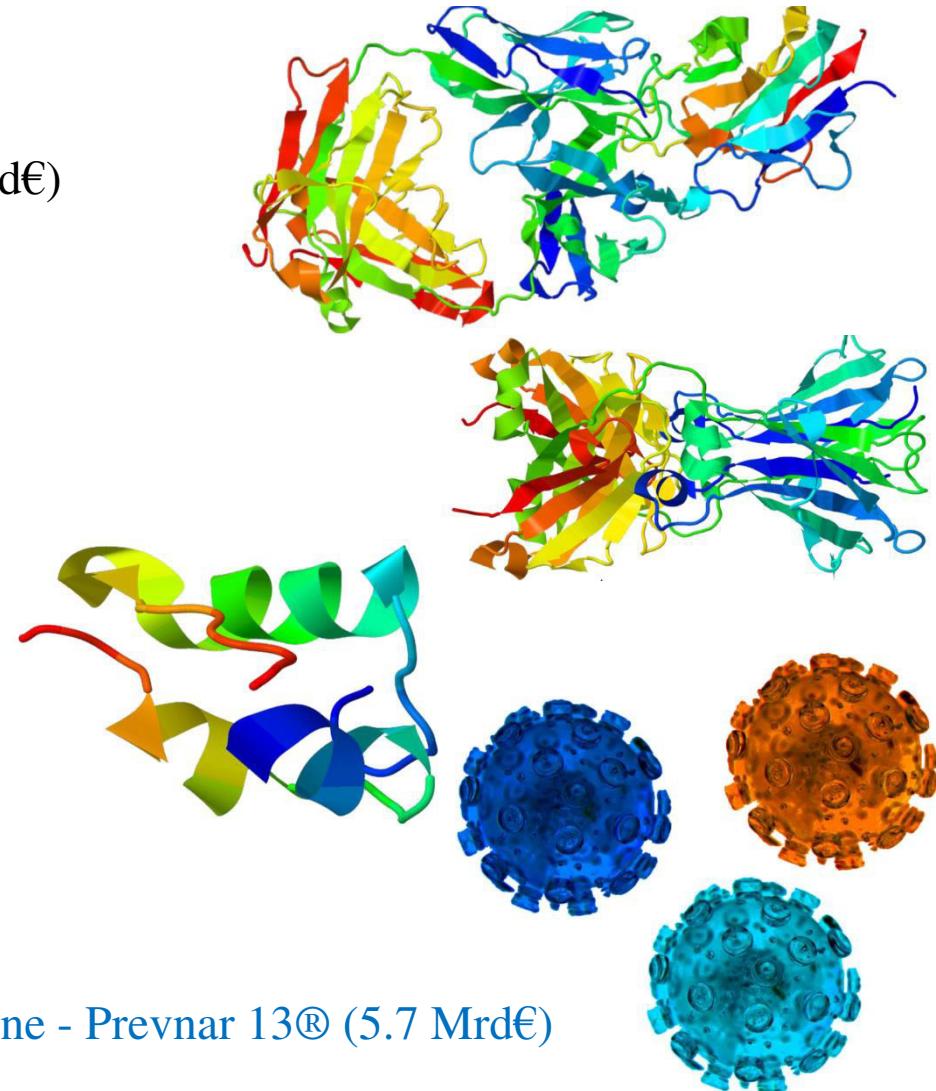
6 Lenalidomide - Revlimid® (7 Mrd€)

7 Bevacizumab - Avastin® (6.8 Mrd€)

8 Trastuzumab - Herceptin® (6.8 Mrd€)

9 Insulin glargine - Lantus® (5.7 Mrd€)

10 Pneumococall 13-valent conjugate vaccine - Prevnar 13® (5.7 Mrd€)



One of the leading groups in
formulation, processing and analysis
of biopharmaceuticals



Infrastructure - Pharmaceutical Technology and Biopharmaceutics



- Research groups: Prof. Merkel, Prof. Winter, Prof. Friess
- 1.500 m² ; ~ 40 members

General Infrastructure - Highlights

- Sterile facility with filling machine, lyophilizer in class A, isolator etc.
- Protein formulation handling equipment e.g. TFF, filling and capping equipment
- Processing equipment e.g. LFs, lyophilizers, spray-dryers, cryo-mill, extruders
- Protein analytical equipment e.g. DLS plate reader, Protein-DSCs, Bio-FT-IR, Fluorescence spectrometer, LCs, FPLCs, AF4s
- Parenteral analytical equipment e.g. Light obscuration, MFI/Flow Cam, Osmometers, Injection Force Measurement
- Further analytical equipment e.g. DSC, TG, DVS, Karl-Fischer, Zetasizer, Laser Diffraction, Cascade impactor

Protein Aggregation - Mechanisms and Analytics

Protein-Protein-Interactions -
Analytics, Protein Effects,
Formulation Effects



Protein Drug Delivery -
Parenteral, Pulmonary,
Topical

Protein-Material-Interactions -
Adsorption, Surfactant Effects

Freeze-Drying -
Process and Formulation
Understanding, PAT Tools

Selected Publications



**Shaken, Not Stirred: Mechanical Stress Testing
of An IgG1 Antibody**

**How Subvisible Particles Become Invisible—Relevance
of the Refractive Index for Protein Particle Analysis**

**Temperature-Ramped Studies on the Aggregation, Unfolding,
and Interaction of a Therapeutic Monoclonal Antibody**

The freezing step in lyophilization: Physico-chemical fundamentals, freezing methods and consequences on process performance and quality attributes of biopharmaceuticals

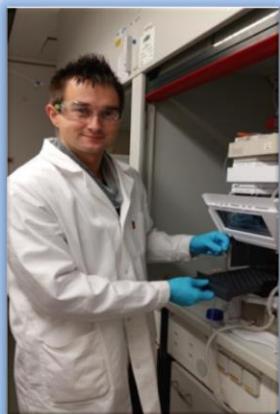
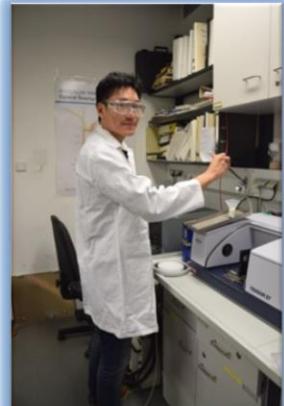
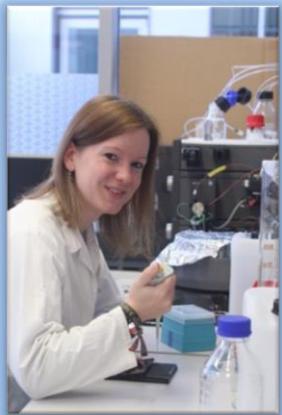
Energy Transfer During Freeze-Drying in Dual-Chamber Cartridges

IgG1 Adsorption to Siliconized Glass Vials—Influence of pH, Ionic Strength, and Nonionic Surfactants

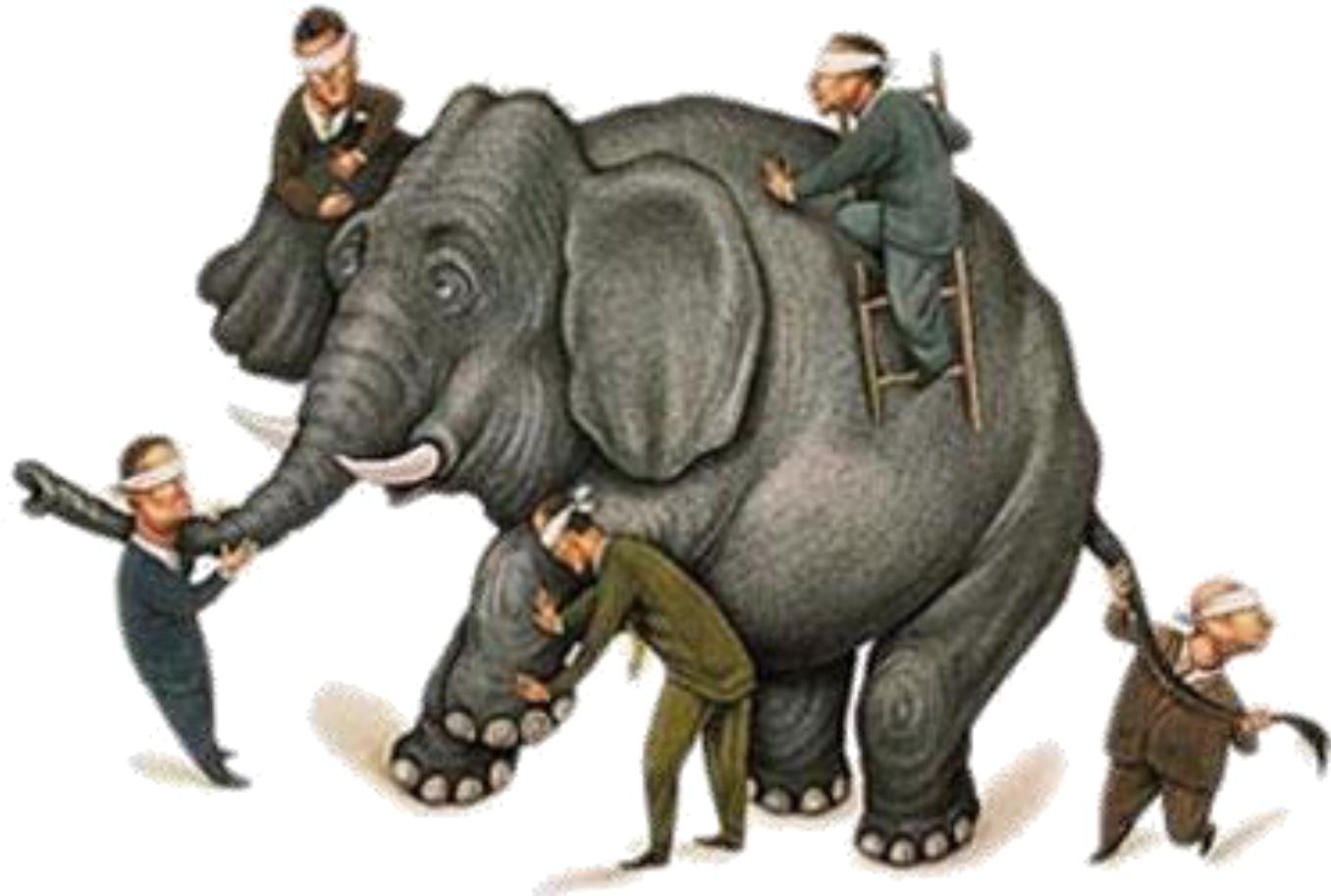
Analysis of thin baked-on silicone layers by FTIR and 3D-Laser Scanning Microscopy **Influence of particle shedding from silicone tubing on antibody stability**

Collagen sponges for bone regeneration with rhBMP-2
Stabilization of IgG1 in spray-dried powders for inhalation

Ph.D. Students And Their Projects



Formulation of Biopharmaceuticals





Development of Delivery Systems for Macromolecules

AK Merkel

Pharmaceutical Technology

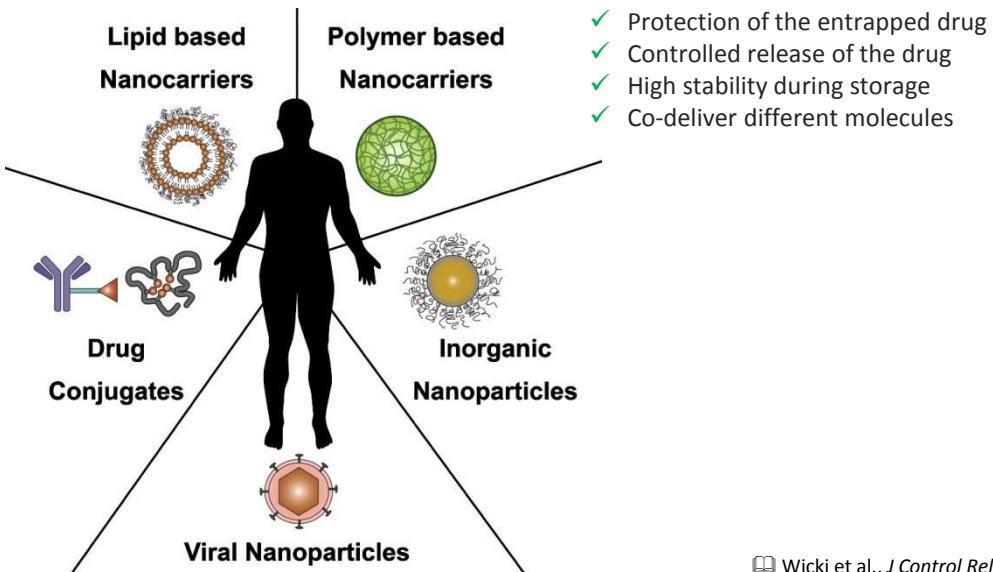
Therapeutic Macromolecules & Drug Delivery Strategies



The use of macromolecules (such as DNA, RNA and Proteins) as therapeutic agents has come to the forefront in recent years. The combination between their poor pharmacokinetics properties and multiple biological barriers stand between the macromolecular drug and its ultimate biological target results in limited therapeutic application

- ✓ Rapid degradation
- ✓ Inability to penetrate target tissues
- ✓ Fail to permeate cell membrane

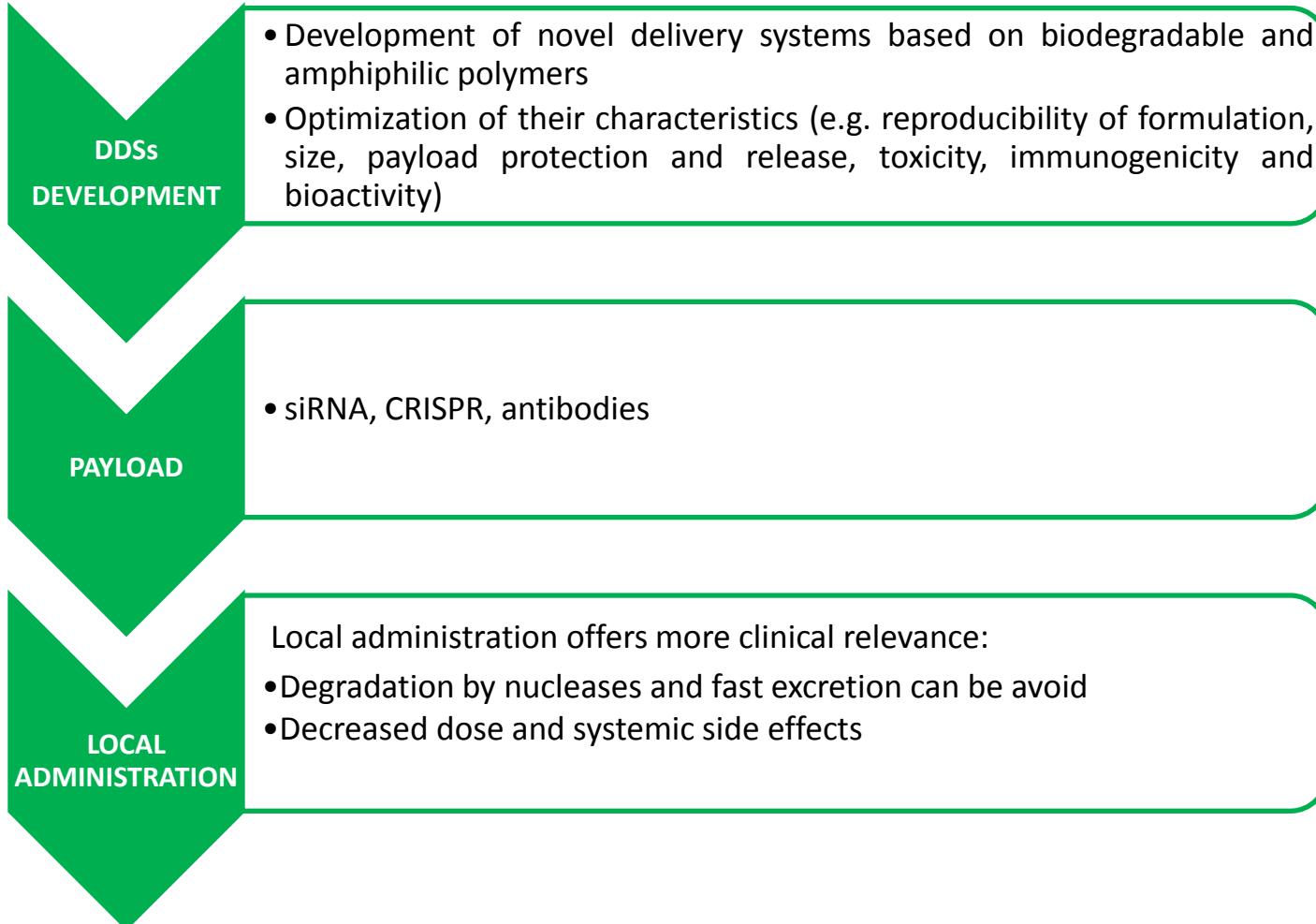
Drug Delivery Strategies (DDSs)



Wicki et al., *J Control Release*. 200:138-57, 2015



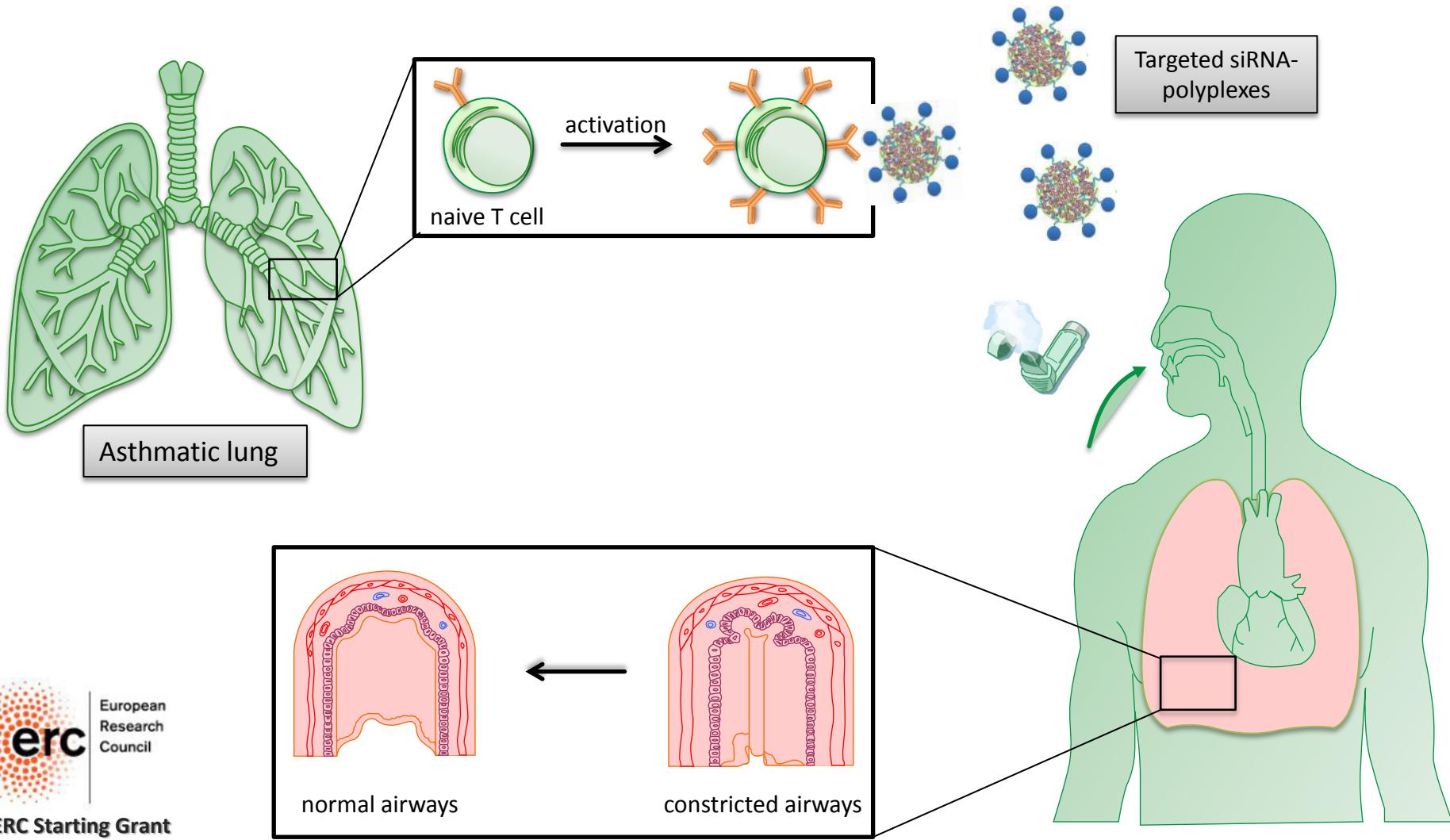
Research Topic



Our goal is to develop novel and clinically relevant nanomedicines for therapy of a range of diseases (Asthma and Cancer with a specific focus on chemosensitization)

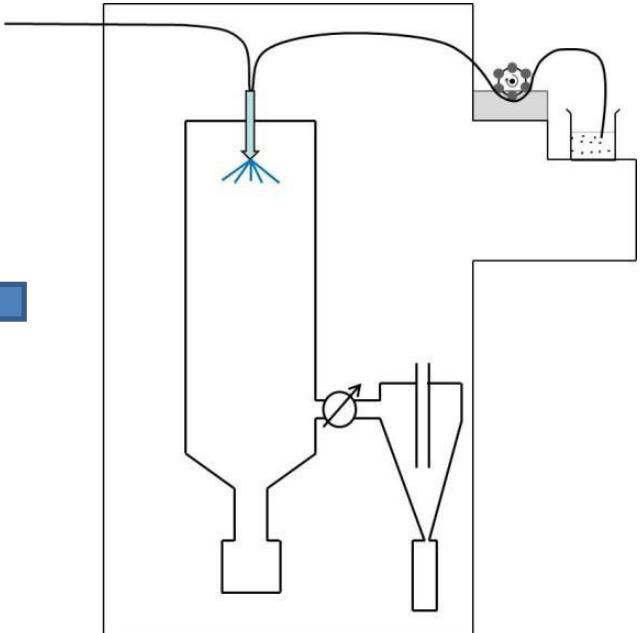
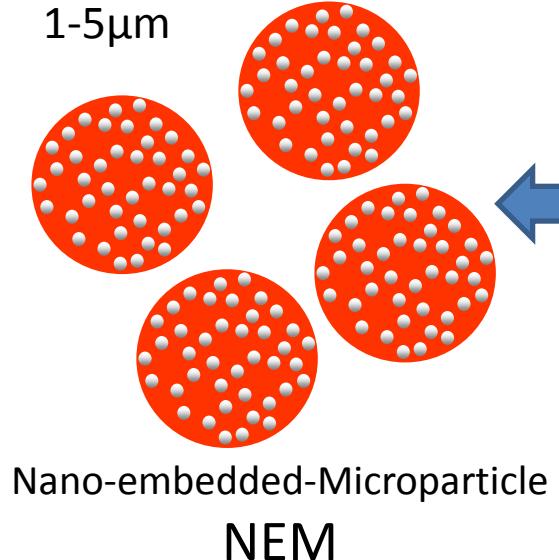
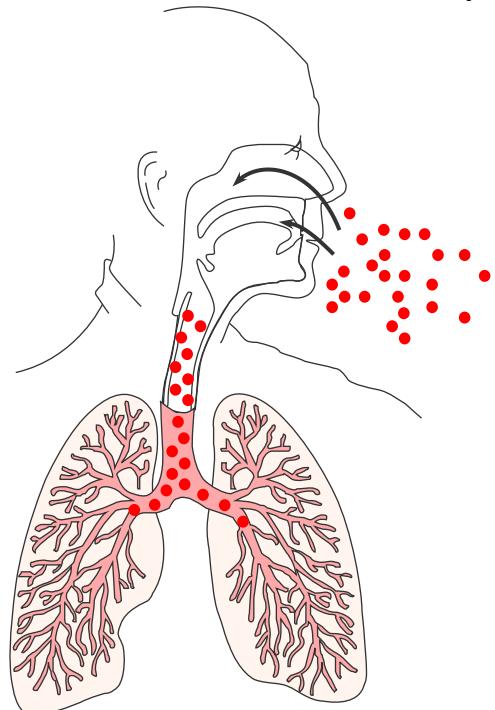
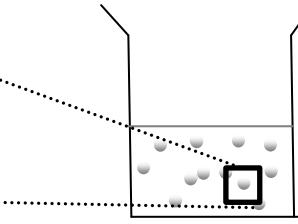
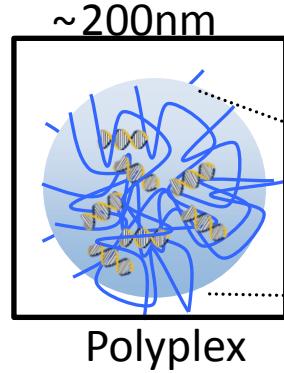
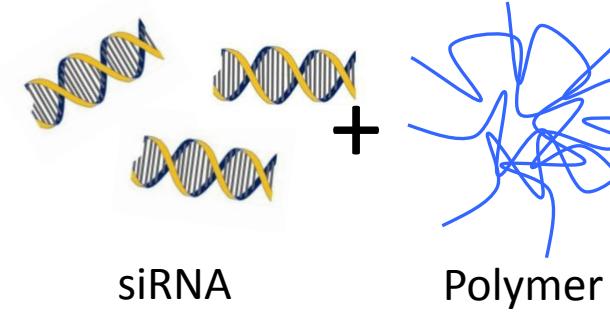
Novel Asthma Therapy

Task1: siRNA delivery to activated T-cells



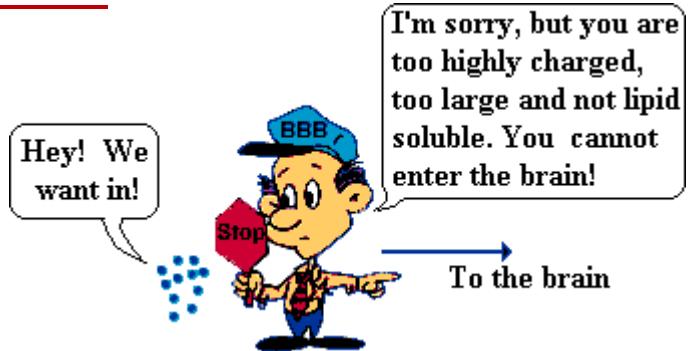
Novel Asthma Therapy

Task2: Nano-embedded-Microparticles

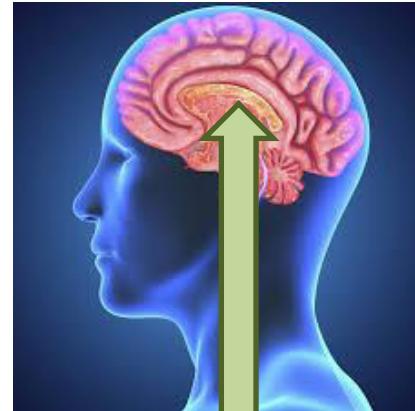


New Delivery Systems to overcome the Blood Brain Barrier

Problem

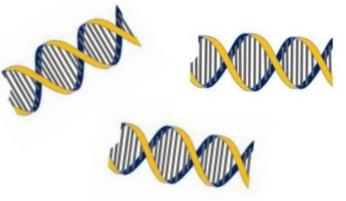


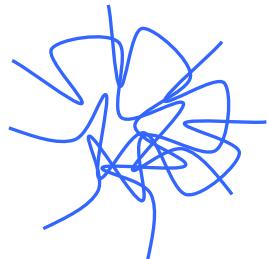
Drugs for brain diseases

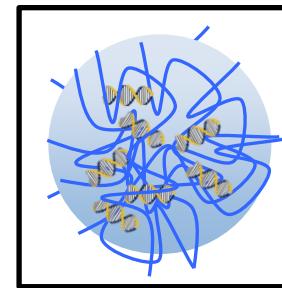


Able to overcome the
Blood Brain Barrier

Solution


siRNA Drugs for brain
diseases

+ 
Polymer

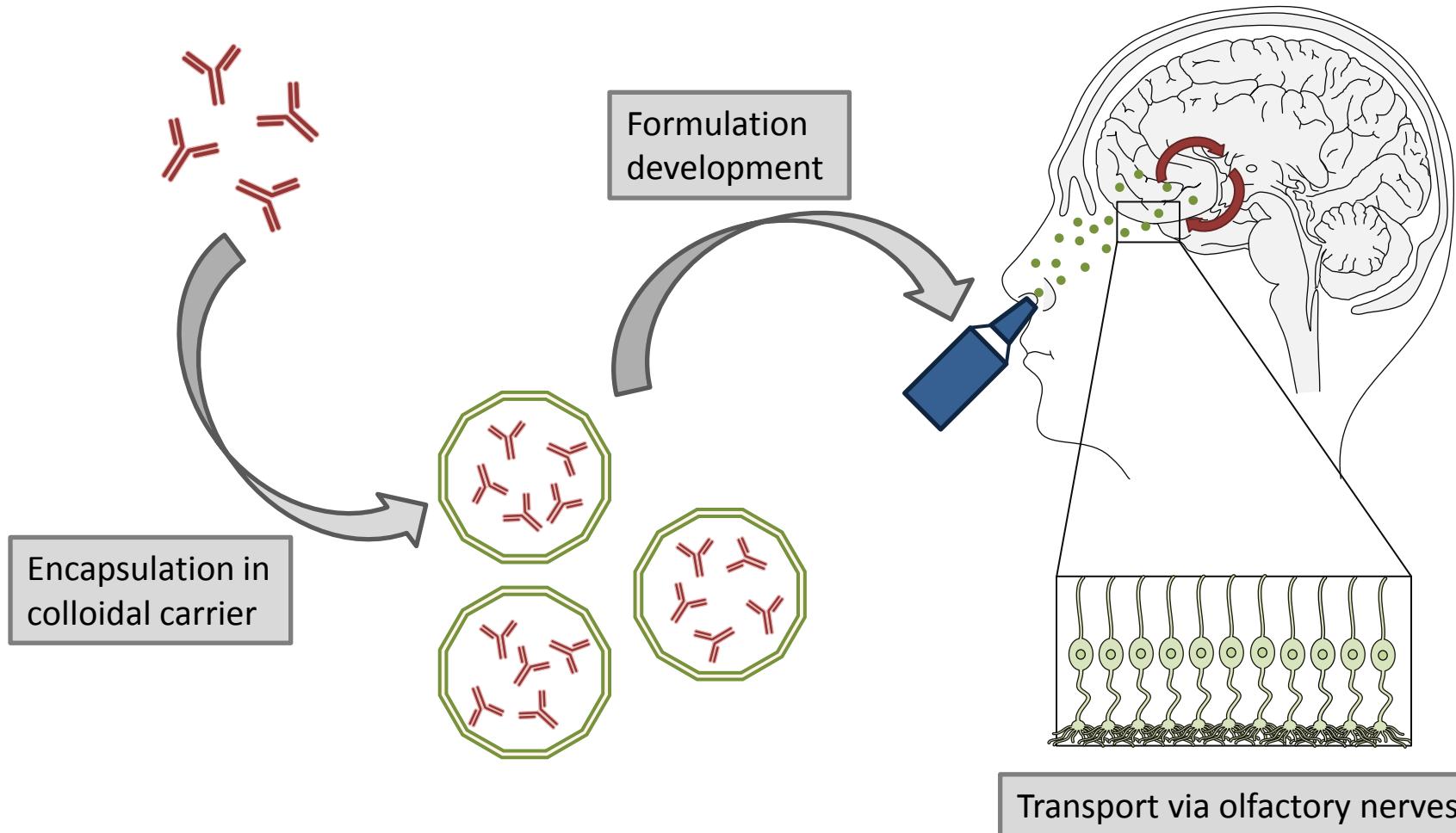


Polyplex





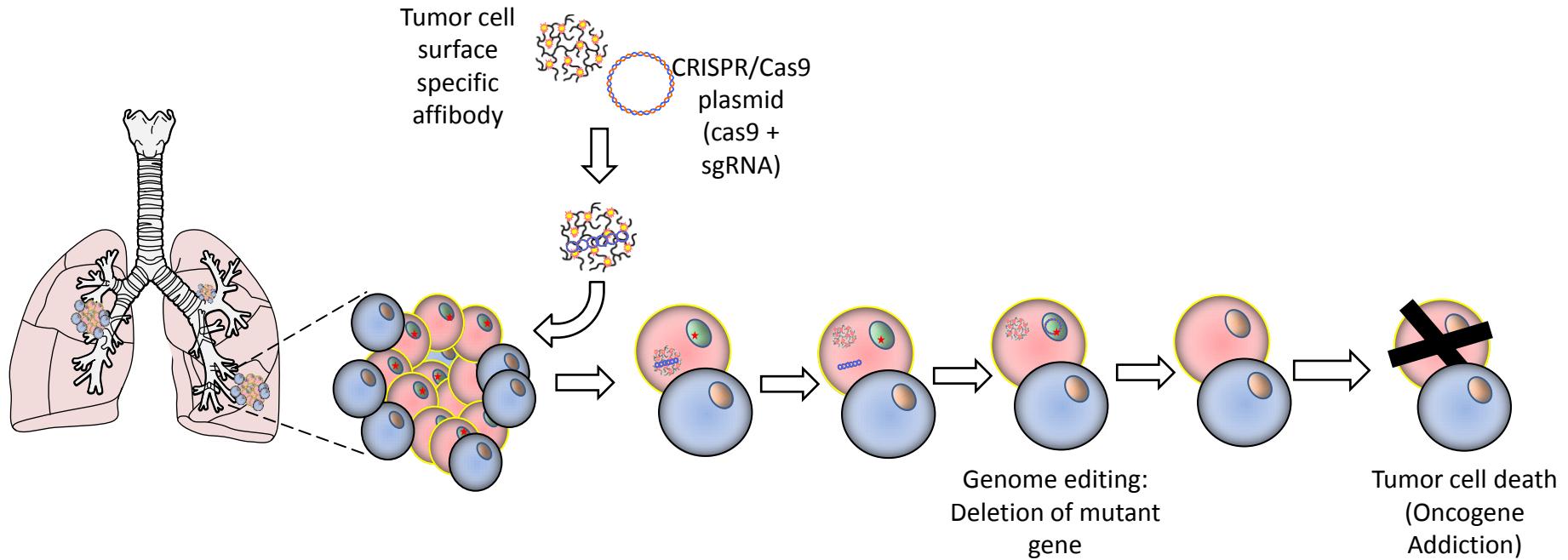
Nose-to-Brain Delivery of Biologicals



abbvie



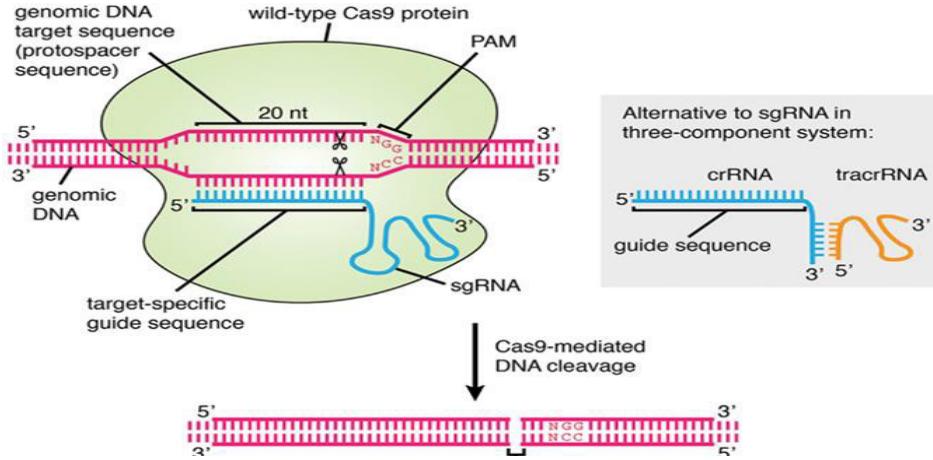
Inhalable nanoparticles for in-vivo genome editing mediated by crispr-cas9 in lung cancer



Development of Myoblast-targeted BSA-based CRISPR-Cas9 Delivery Systems

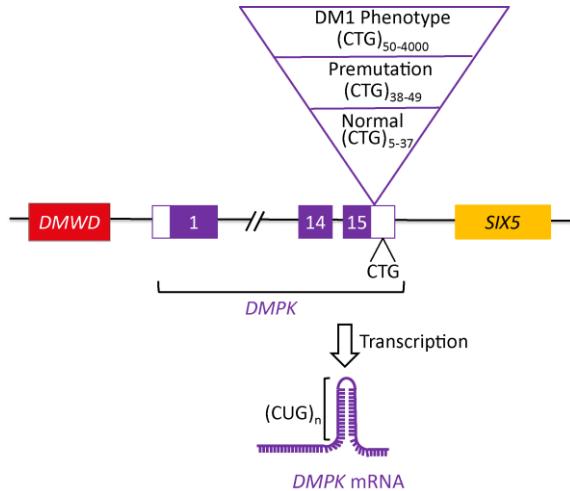


Genome editing by CRISPR-Cas9

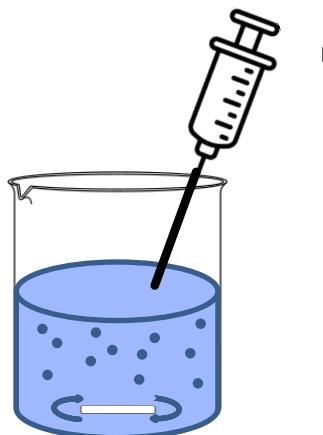


Myotonic dystrophy type 1 (DM1) is caused by $(CTG \cdot CAG)_n$ -repeat expansion within the DMPK gene

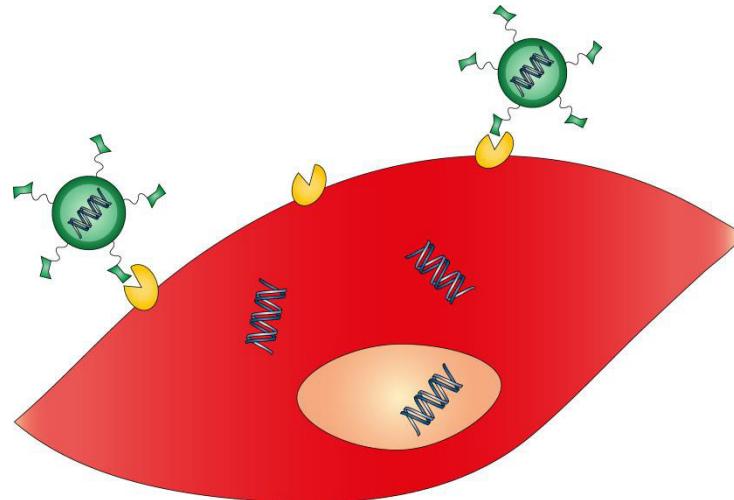
Perfect Target for the application of CRISPR-Cas9 technology



Formulation of BSA-based Nanoparticles

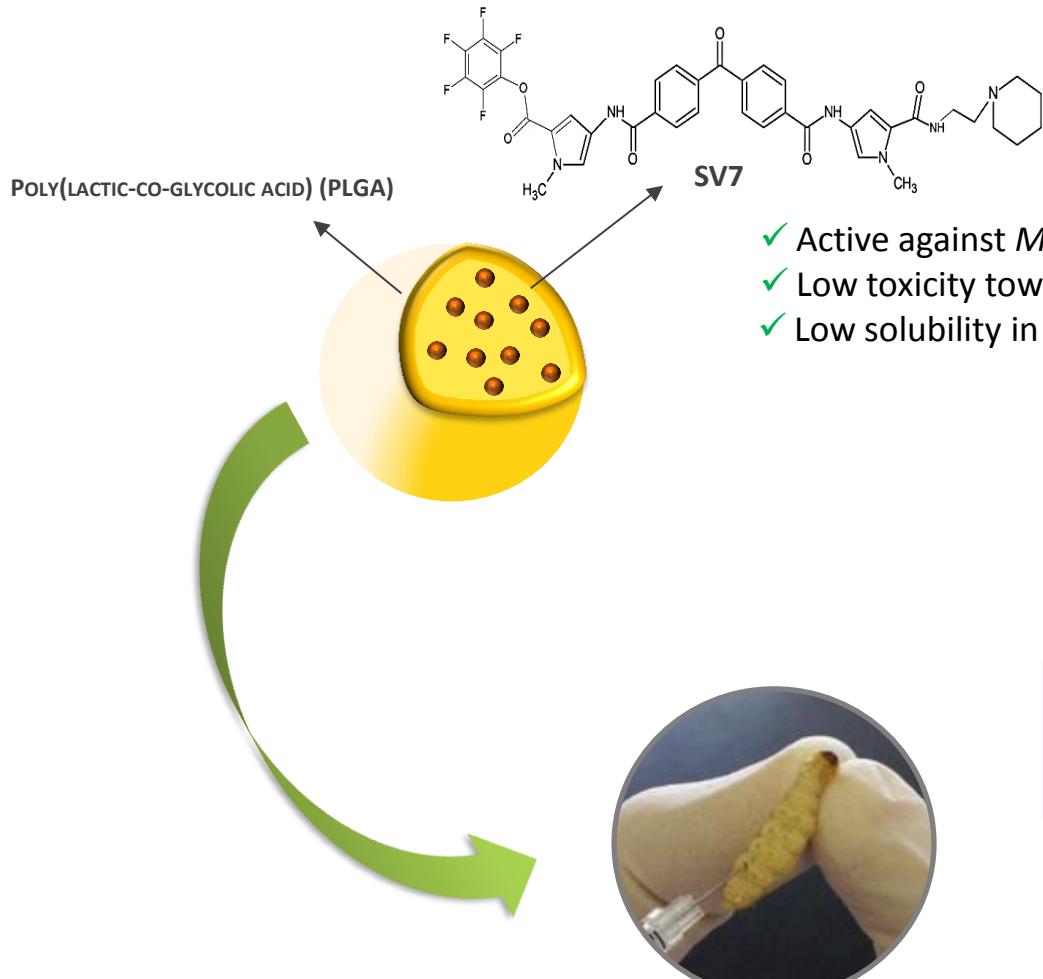


Functionalized –Nanoparticles can be internalized by receptors that are on the surface of myoblast and allow an efficient delivery of the nucleic acid





G. mellonella model to evaluate the efficacy *in vivo*



- ✓ Active against *Methicillin Resistant S. aureus*
- ✓ Low toxicity towards mammalian cells
- ✓ Low solubility in water phase

Vooturi S.K. et al., *J. Med. Chem.*, 52 (16) 5020-5031, 2009.
 Vooturi S.K. et al., *Org. Biomol. Chem.*, 9 (18), 6367-6372, 2011.

Rapid model for screening novel antimicrobial agents in order to predict clinical outcomes

G. Mellonella infection model



AK Merkel

Prof Dr. Olivia Merkel

Dr. Gabriella Costabile

Dr. Aditi Mehta

Tobias Keil

Natascha Hartl

Rima Kandil

Lorenz Isert

Bettina Schwarz

Matteo Petrini (*Klinikum der Universität München*)

Patrick Strack (*Boehringer Ingelheim*)

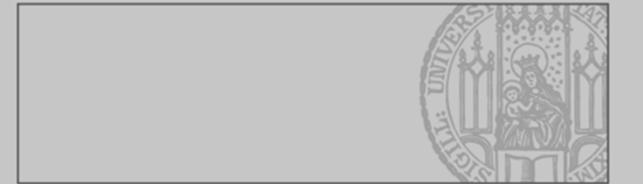
Elena Dalle Vedove (ERASMUS+Intern)





Pharmaceutical Technology und Biopharmaceutics

- 3 Professors
- 6 senior scientists
- ca.40 Ph.D students



Arbeitsgruppe Gerhard Winter

Research Day
1.12.2017



Pharmacy - University of Heidelberg 1977-82

Ph.D. in Pharm. Technol. (transdermal) 83-87

Lab head at Merck, Darmstadt 87-88

Positions at BM, later Roche, Mannheim 88-99

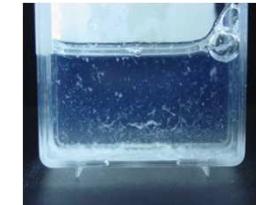
(heading department for parenteral drug formulations,
incl.proteins (EPO, rPA, Ibandronate, GCsf, mAbs)

Professor at the LMU 2000 -present

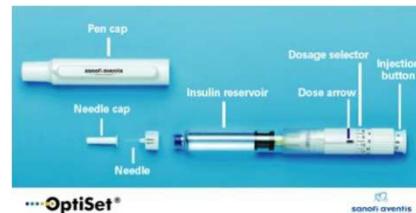
2008 Co-founder of Coriolis Pharma, Martinsried



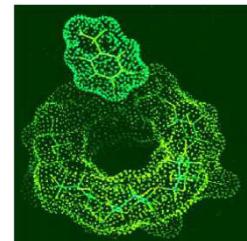
Protein drugs and vaccines



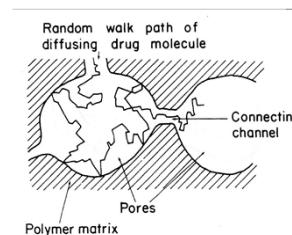
PARENTERAL TECHNOLOGIES



Excipients and Biomaterials



Nanocarriers and depots



Working group 2017



Our PD. team



Michaela Breitsamer
Liposomengele als Proteindepot
Extruder, DAC, Protein/ HS Analytik, Phys.chem Analyten,
Auswertung von Tierversuchen



Simon Eisele
Nasale Arzneiformen für Phagenlysin
Proteinanalytik, Gelformulierungen, Packmitteltests



Julian Gitter
Innovative Gefriertrocknungsverfahren
Gefriertrocknung, Verfahrenstechnik Phys. Analytik;
Proteinanalytik



Bernard Manuel Haryadi
Bio-inspired elongated nanoparticles
Nanoparticle production and analysis



Dennis Krieg
Co-Formulierungen für Pharma-Proteine
HPLC, Spektroskopie, GT



Teresa Kraus
Immunogenität von Proteinaggregaten im
humanen Lymphknotenmodell
Protein Stress Modelle, Filtration, Zellkultur



WeiWei Liu

Systematic release studies with liposome-gels

In vitro release models, DAC, HPH



Ute Rockinger

Gefriertrocknung von humanen Zellen

Zellkultur, Gefriertrocknung,



Andreas Stelzl

Patch pumps für Proteine

Nano coulter counter, patch pump tests



Hristo Svilenov
HT Protein Stabilitätsvorhersage
HT Analytics, Chem Denaturation, Spektroskopie



Andreas Tosstorff
In silico Suche nach „Aggregation-Breakers“
MD Simulationen, Aggregationsstudien an Proteinen



Markus Zang
Neue Verfahren in der Gefriertrocknung
Verfahrenstechnik , GT, neue Packmittel, Nucleation



Geplanten Arbeitsgebiete :
„Virus-Galenik“ zusammen mit Biel/Michalakis
Simulationen in der Pharm. Technologie

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Website /Pub med / researchgate
Schaukasten Publikationen Haus B, 1. OG, Flur – Ostseite

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„Kurzbericht und Kurzreferat gehören als Trainingselement zur ersten selbstständigen wissenschaftlichen Arbeit.“