



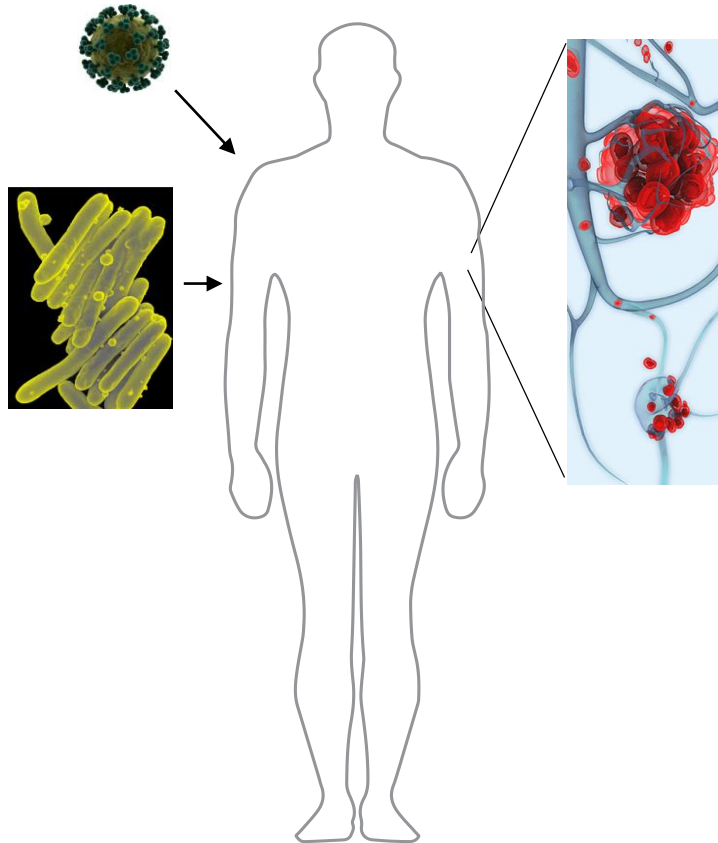
Exploiting the Human Peptidome for Novel Antimicrobial and Anticancer Agents



On-site evaluation
Feb. 1st and 2nd, Ulm



Infectious diseases and cancer



- **Major causes of death**

Infections: ~15 million

Respiratory infections: ~5 million

HIV/AIDS: ~1.1 million

Tuberculosis: ~1.4 million

Cancer: ~8 million

Caused by infections: ~2 million

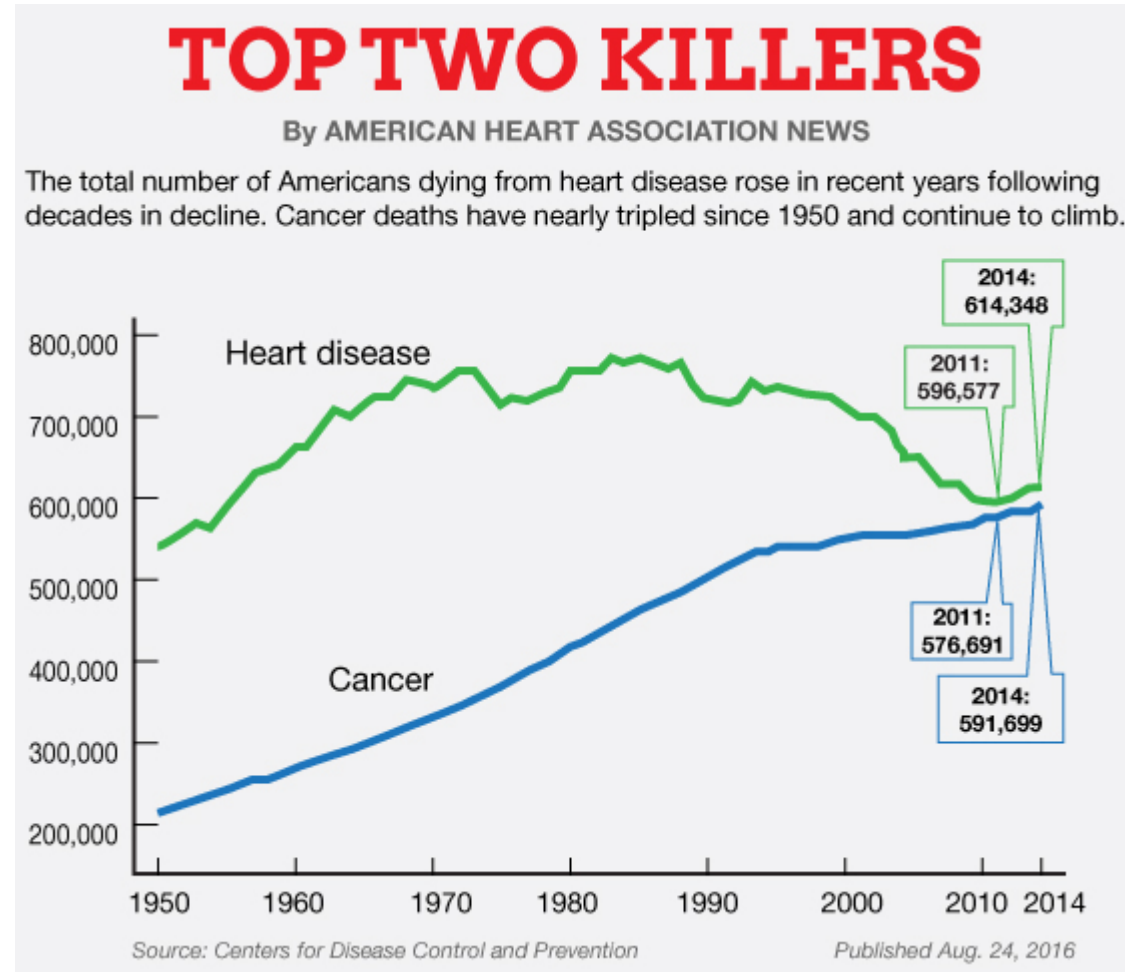
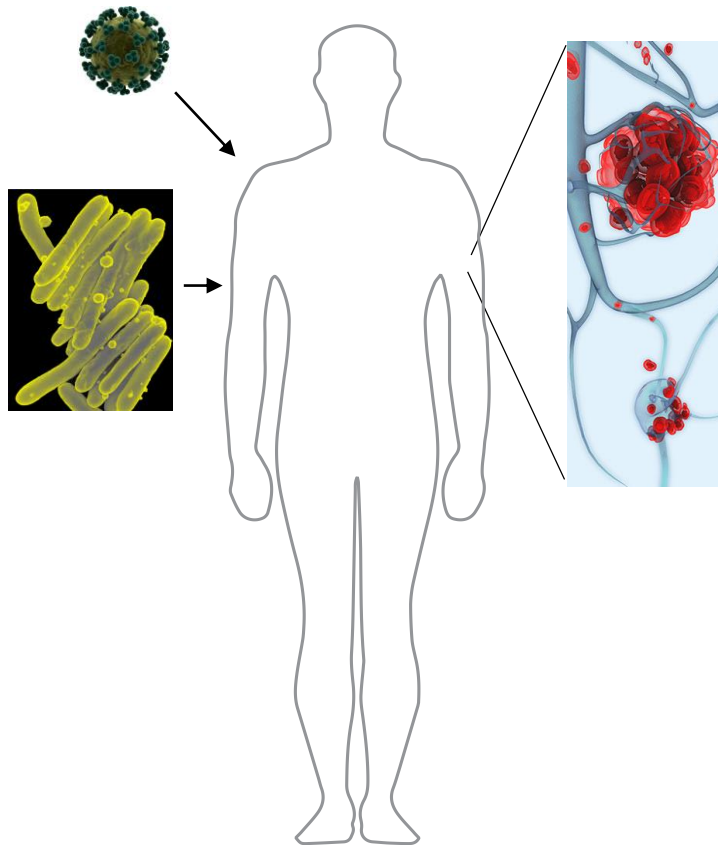
Leukemia: ~300.000

Pancreatic cancer: ~300.000

Source: WHO global health reports



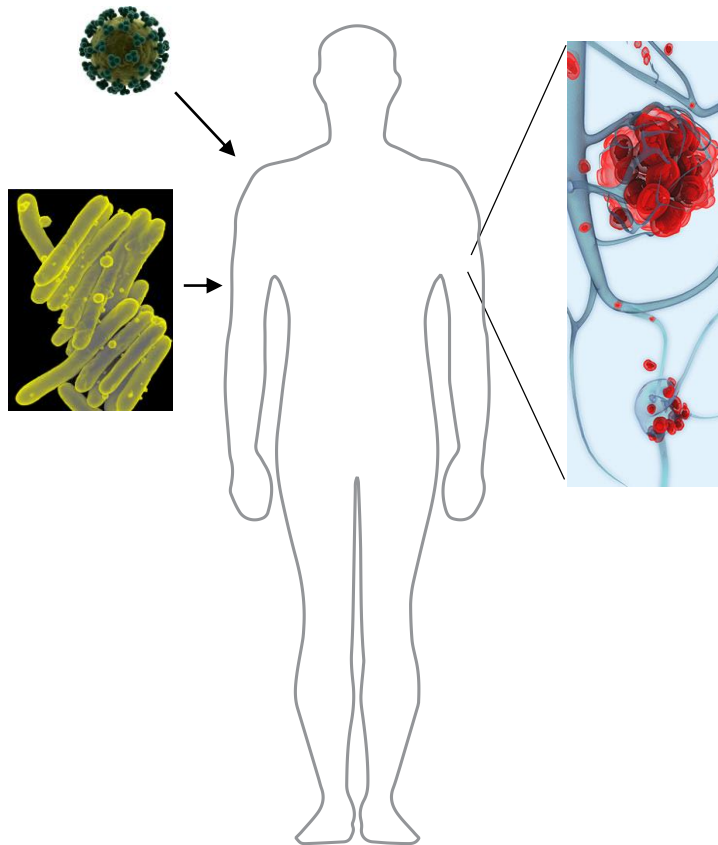
Infectious diseases and cancer



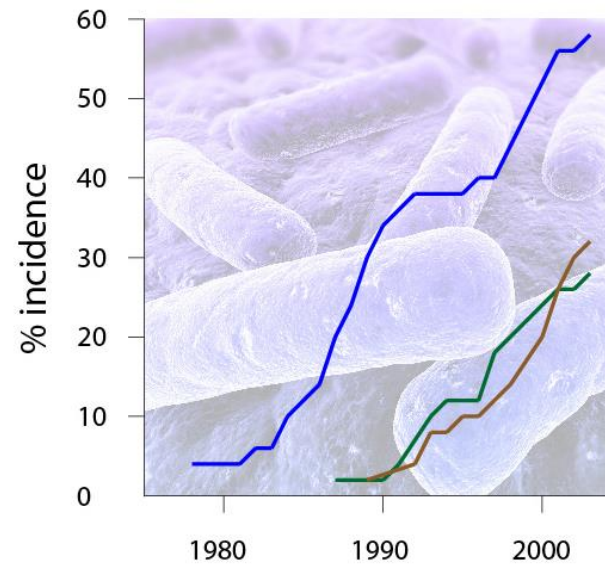


Infectious diseases and cancer

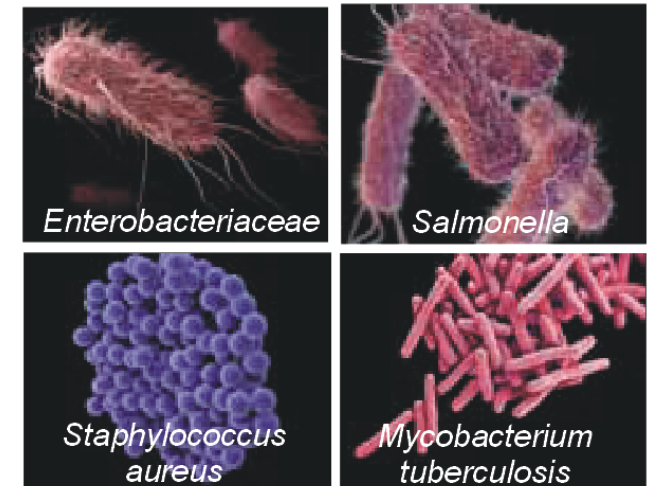
- Major causes of death
- **Difficult to treat**



Antibiotic-resistant infections



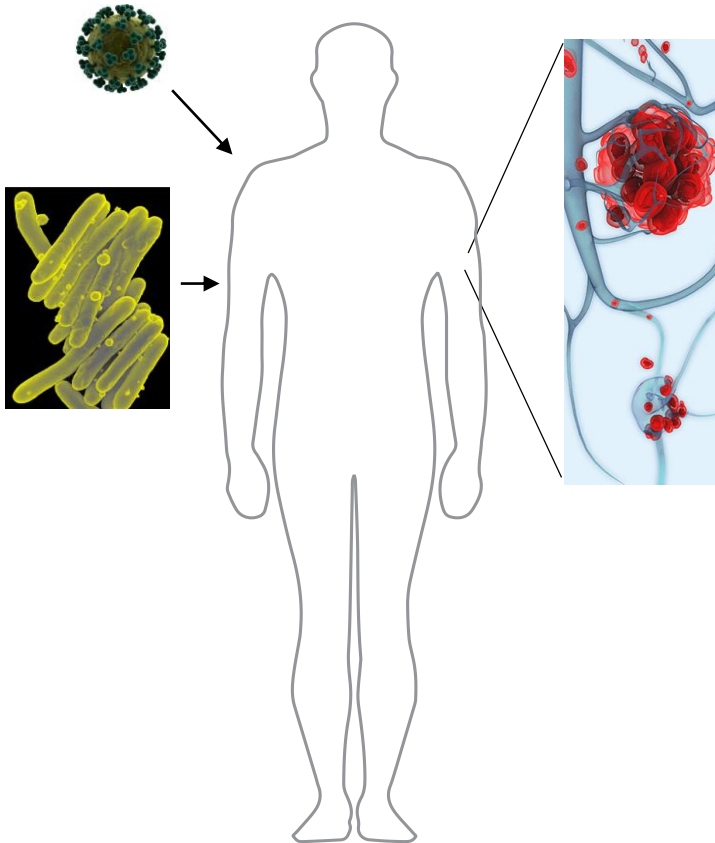
Source: Centers for Disease Control and Prevention



Source: CDC report 2015



Infectious diseases and cancer

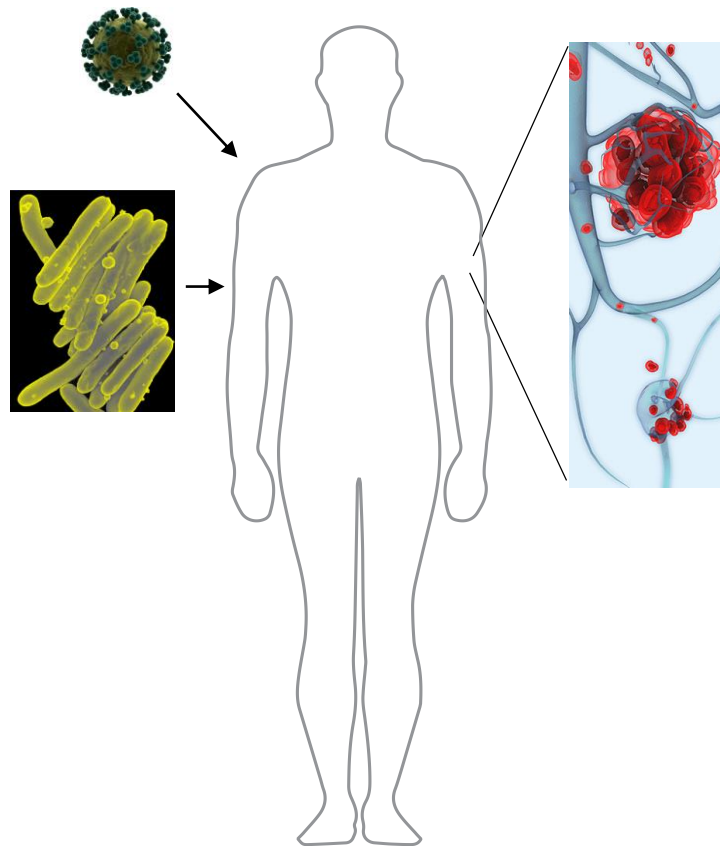


- Major causes of death
- **Difficult to treat**

Improved treatments and a better understanding of our defense mechanisms are urgently needed

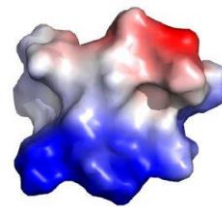


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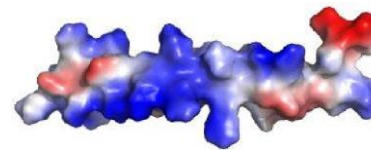


- Major causes of death
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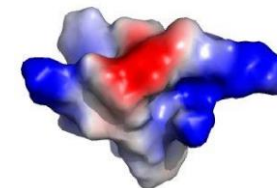
Many endogenous peptides inhibit pathogens and eliminate infected and cancer cells



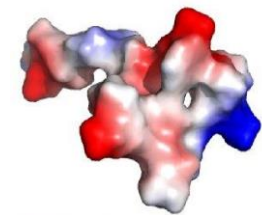
EPI-X4



LL-37



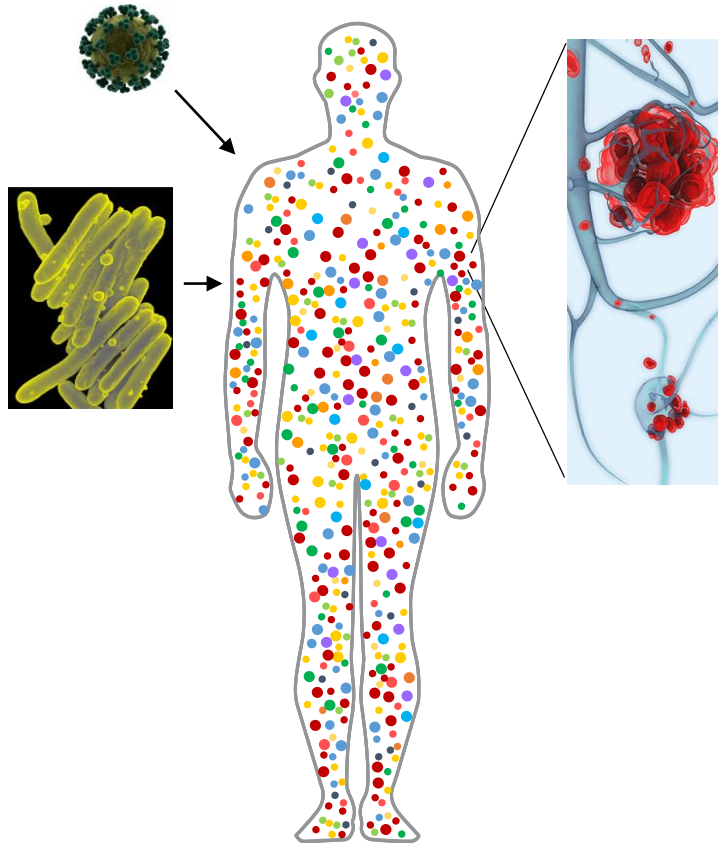
Somatostatin



VIRIP

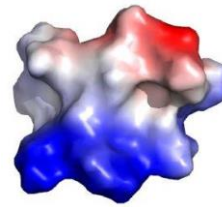


Infectious diseases and cancer

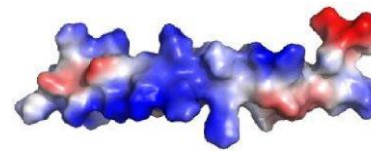


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- **Difficult to treat**

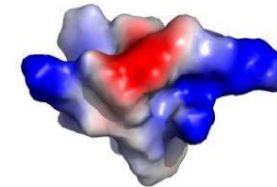
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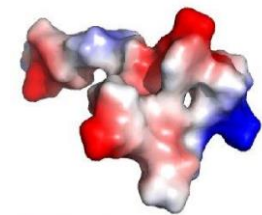
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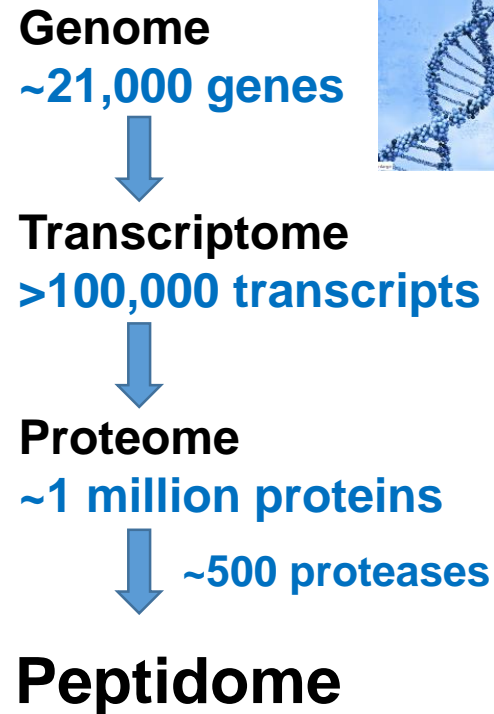
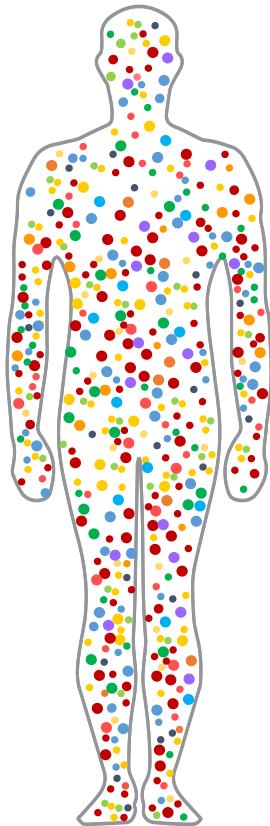
Somatostatin



VIRIP



Endogenous peptides: exploiting the human peptidome

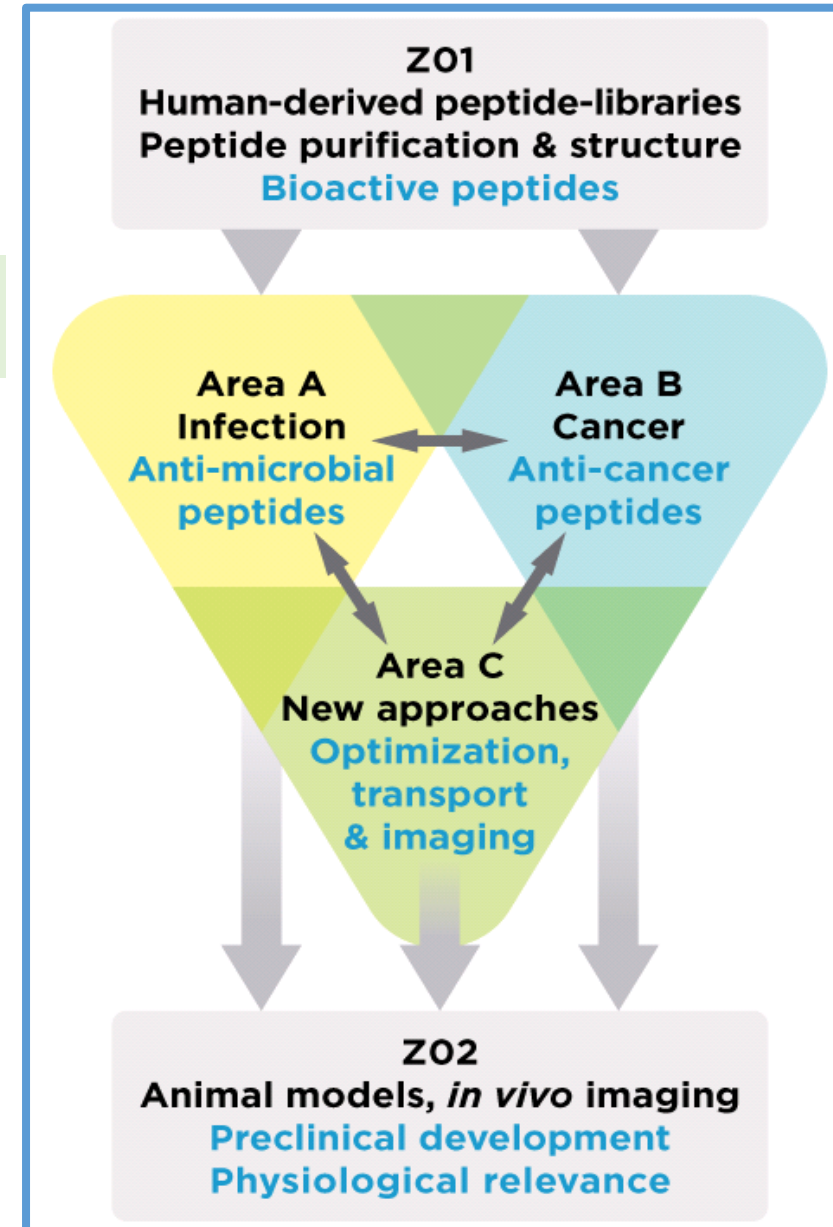
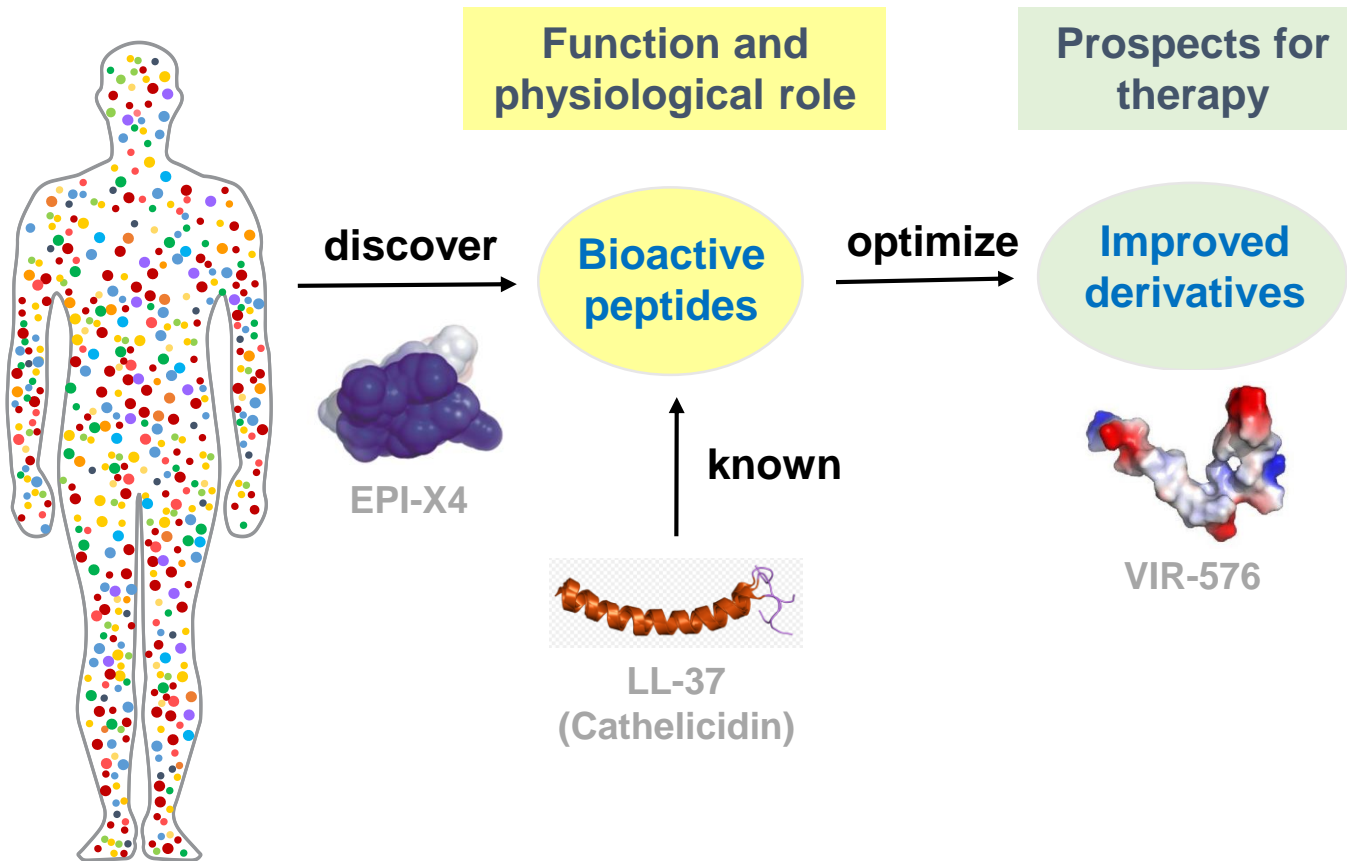


- **Enormous complexity**
- **Governs many processes**
- **Key role in immunity & cancer**
- **Many antimicrobial peptides (AMPs)**
- **Functionally hardly explored (<1%)**

→ **“Gold mine”** for novel discoveries

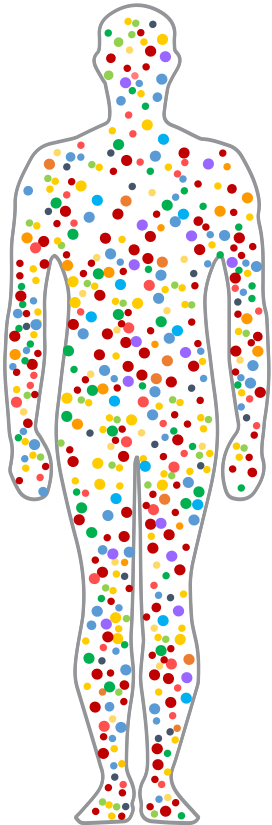


Functional peptidomics





Z01: making the peptidome accessible



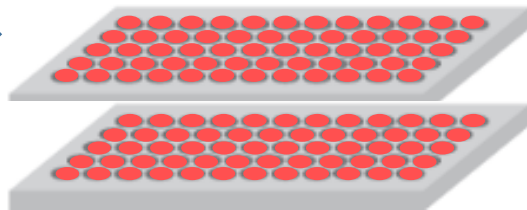


Z01: making the peptidome accessible

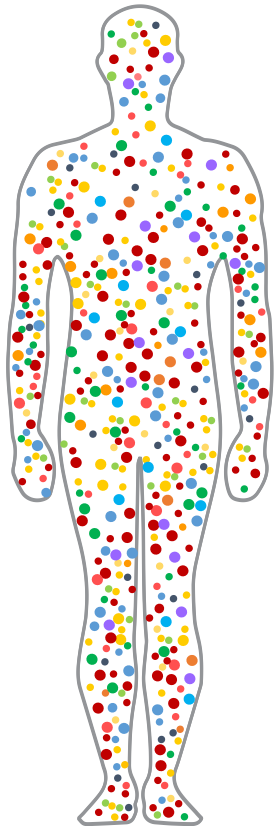
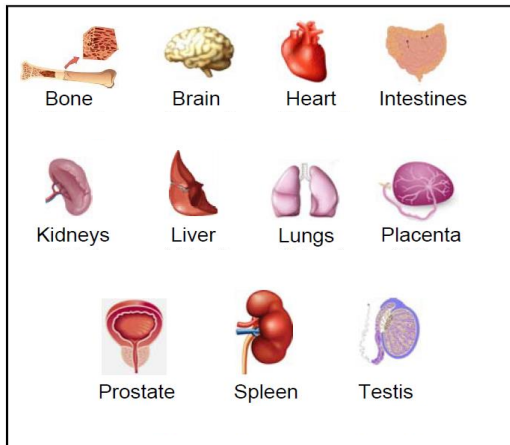


Ludger Ständker
Core Functional Peptidomics

Peptide library
~300 fractions
highly concentrated



Tissues and body fluids





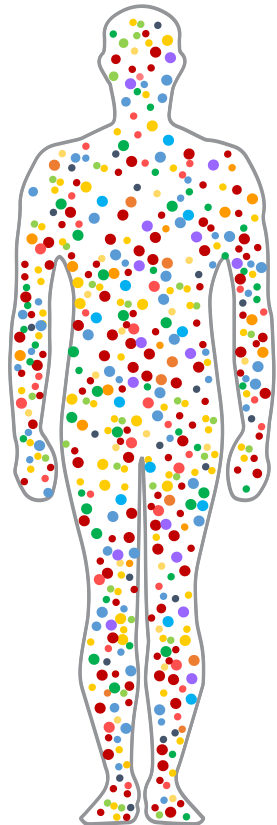
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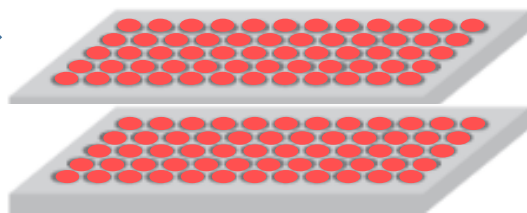
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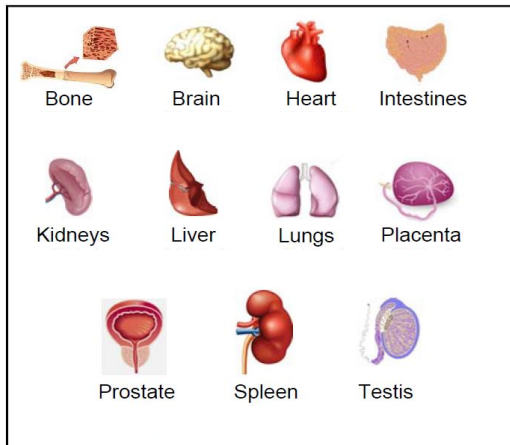
Sebastian Wiese
Core MS & Proteomics



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highly concentrated



Tissues and body fluids



A & B: bioassays
Antimicrobial and
Anticancer activity



**Discovery
Purification**

Bioactive peptides



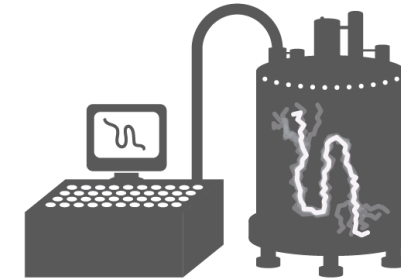
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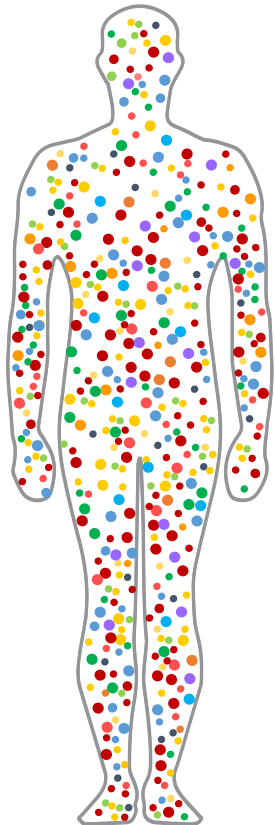
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Core MS & Proteomics



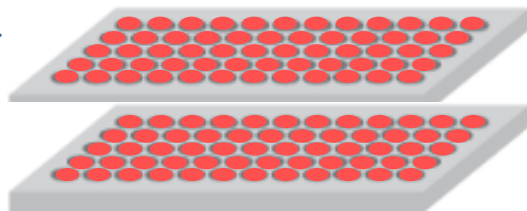
NMR structure



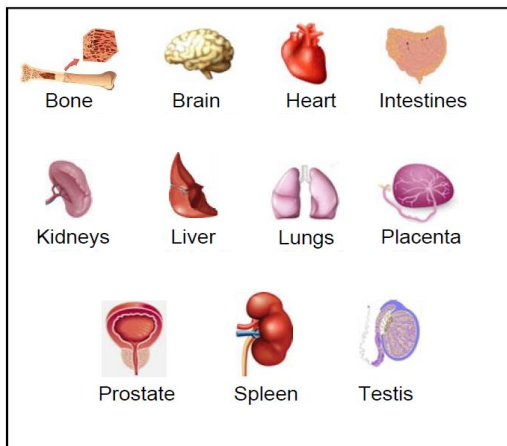
Manfred Wagner
MPIP, Mainz



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Tissues and body fluids



A & B: bioassays
Antimicrobial and
Anticancer activity

**Discovery
Purification**

Bioactive peptides



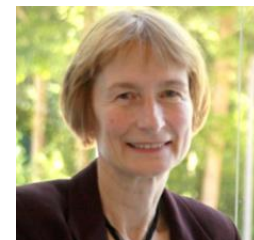
Advanced modeling



Timo Jacob
Electrochemistry



**TEM microscopy
Peptide imaging**



Ute Kaiser
Electron microscopy



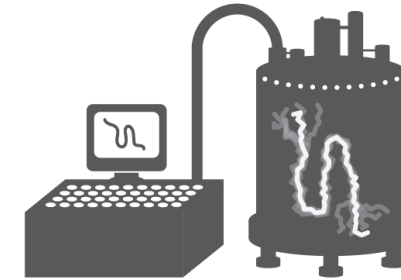
Z01: making the peptidome accessible



Ludger Ständker
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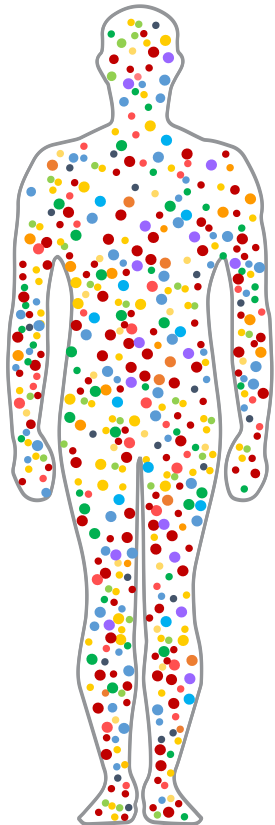
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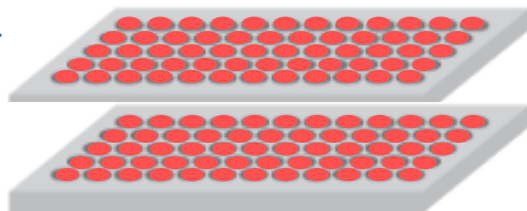
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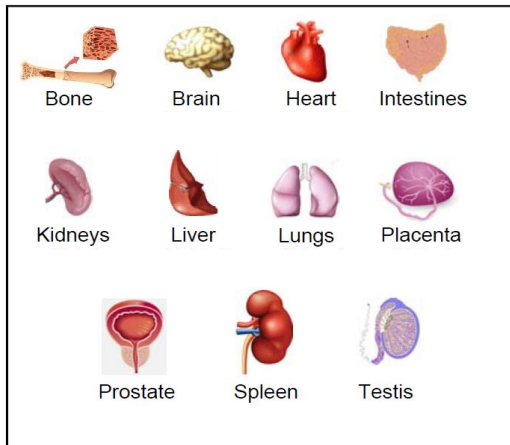
Manfred Wagner
MPIP, Mainz



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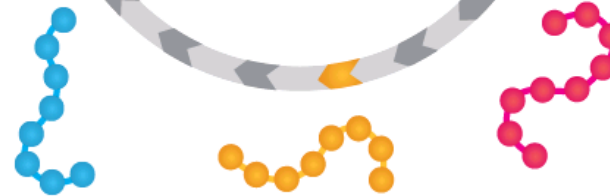


Tissues and body fluids



A & B: bioassays
Antimicrobial and
Anticancer activity

**Discovery
Purification**



Bioactive peptides

Scientific projects
Areas A, B & C



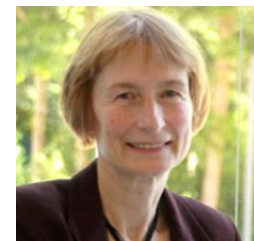
Advanced modeling



Timo Jacob
Electrochemistry



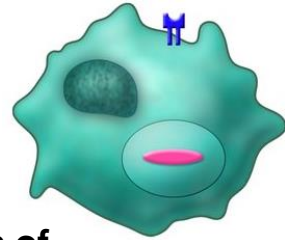
TEM microscopy
Peptide imaging



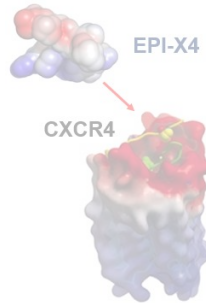
Ute Kaiser
Electron microscopy



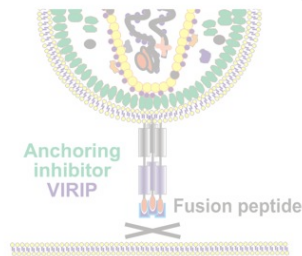
A: Infection



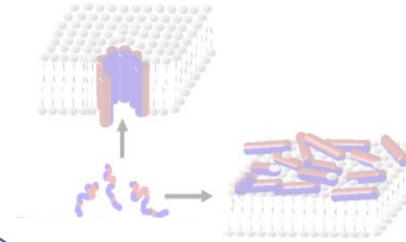
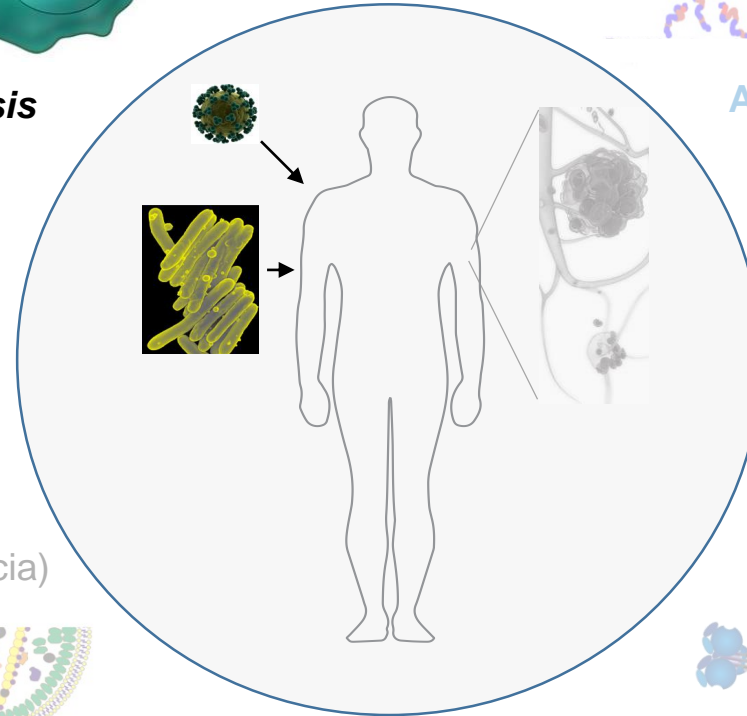
A01: Inhibitors of *Mycobacterium tuberculosis*
(Michaelis, Stenger)



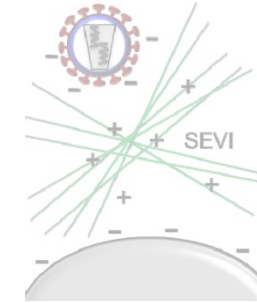
A06: Function of EPI-X4
(Klein, Münch, Sanchez-Garcia)



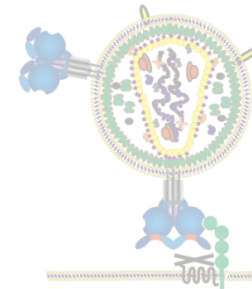
A05: Inhibitors of viral fusion peptides
(Kirchhoff, Weil)



A02: Antimicrobial peptides
(Münch, Spellerberg)



A03: Amyloid peptides
(Fändrich, Münch, Walther)

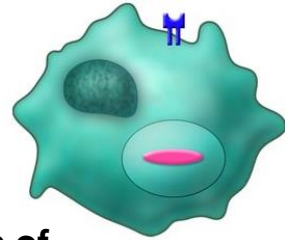


A04: Novel ligands of G protein-coupled receptors
(Kirchhoff)

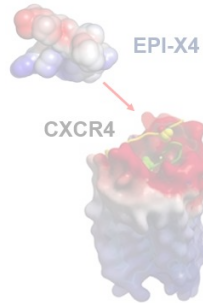


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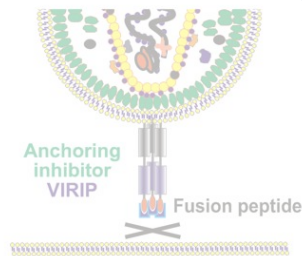
Granulysin,
LL-37, Angiogenin



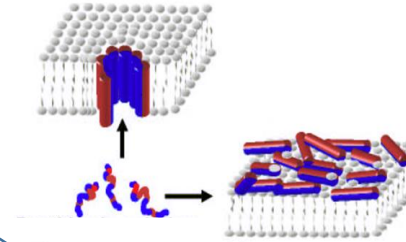
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(Michaelis, Stenger)



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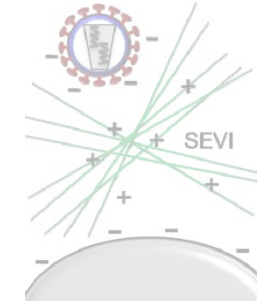


**A05: Inhibitors of
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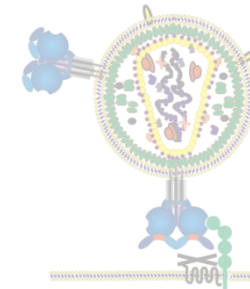


Placental
AMPs

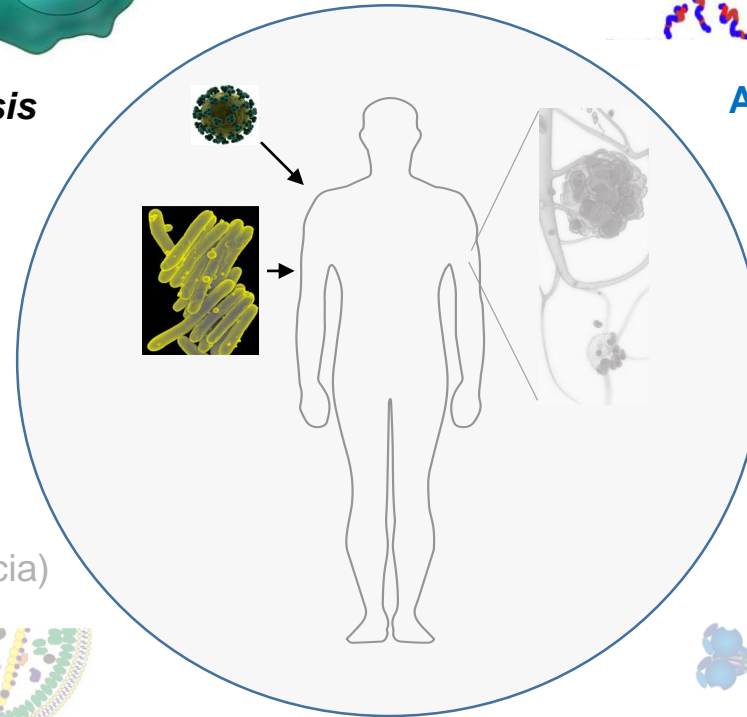
A02: Antimicrobial peptides
(Münch, Spellerberg)



A03: Amyloid peptides
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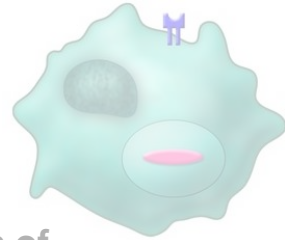


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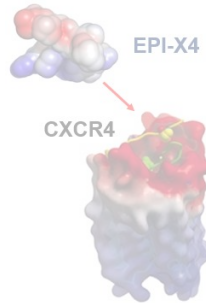




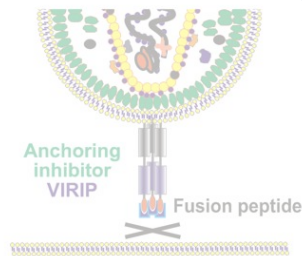
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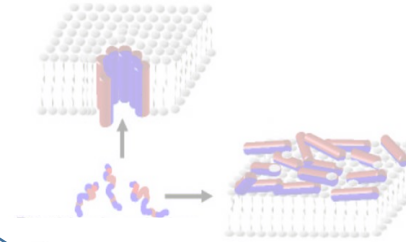
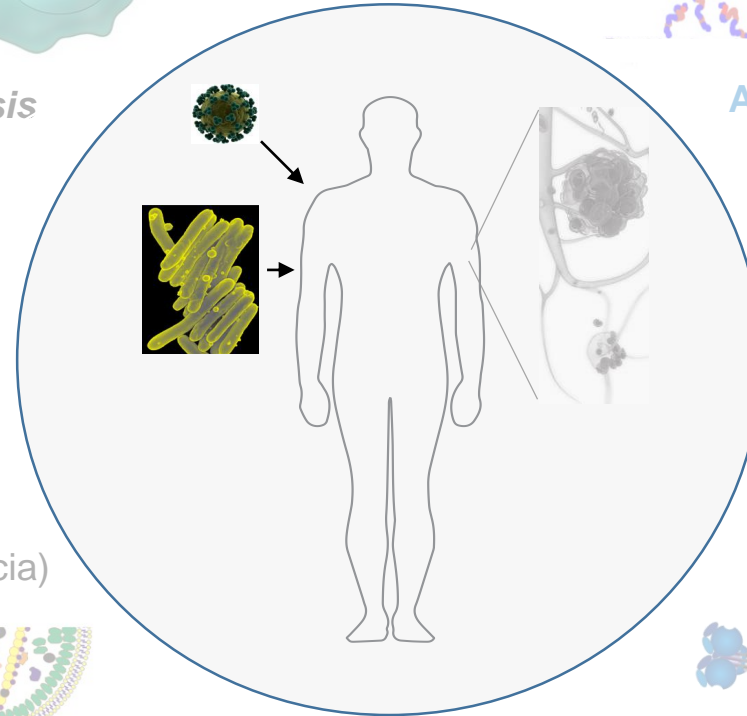
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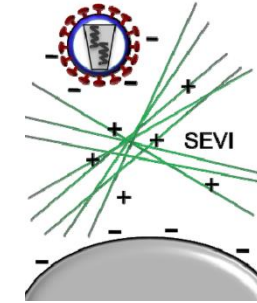
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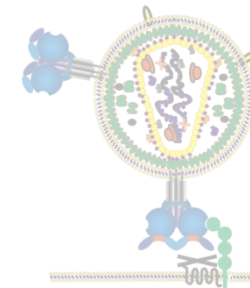


A02: Antimicrobial peptides
(Münch, Spellerberg)



Fibrils enhance viral infection

A03: Amyloid peptides
(Fändrich, Münch, Walther)



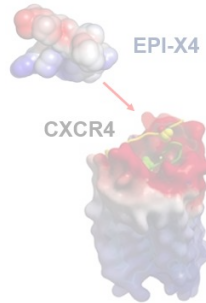
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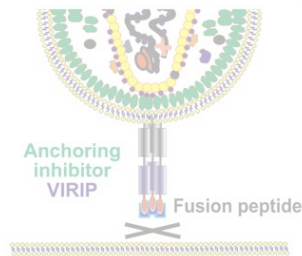
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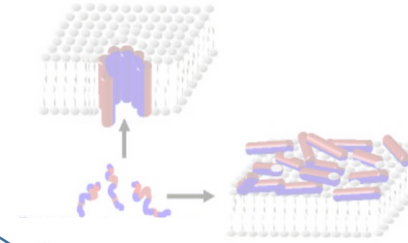
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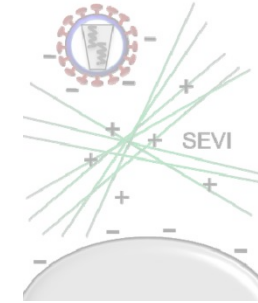
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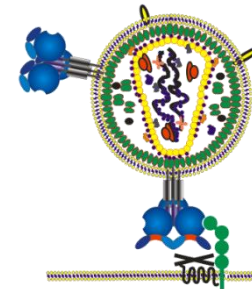
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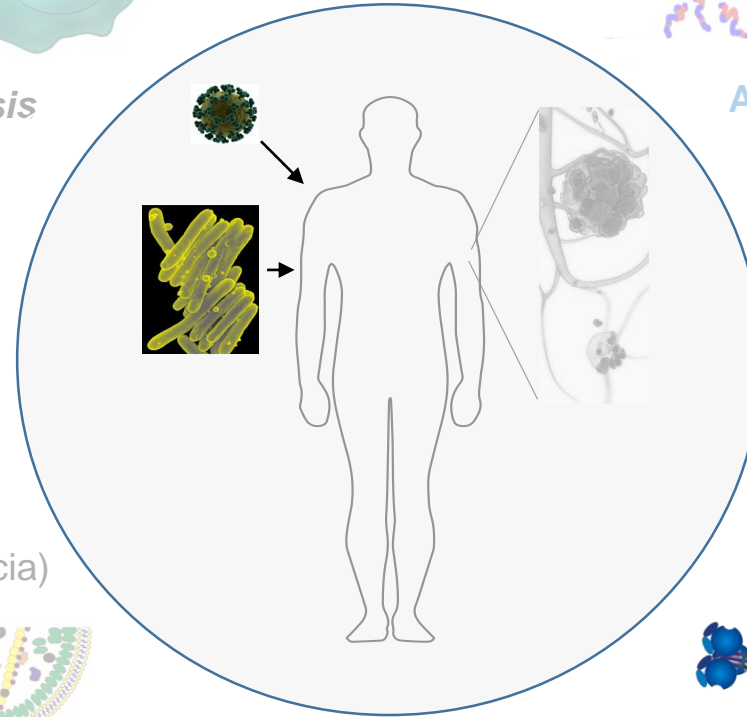
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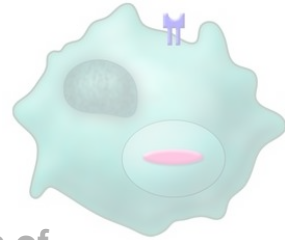


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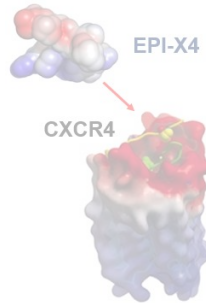




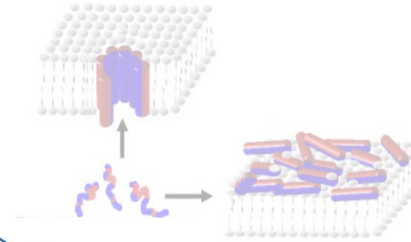
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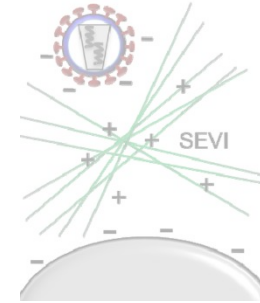
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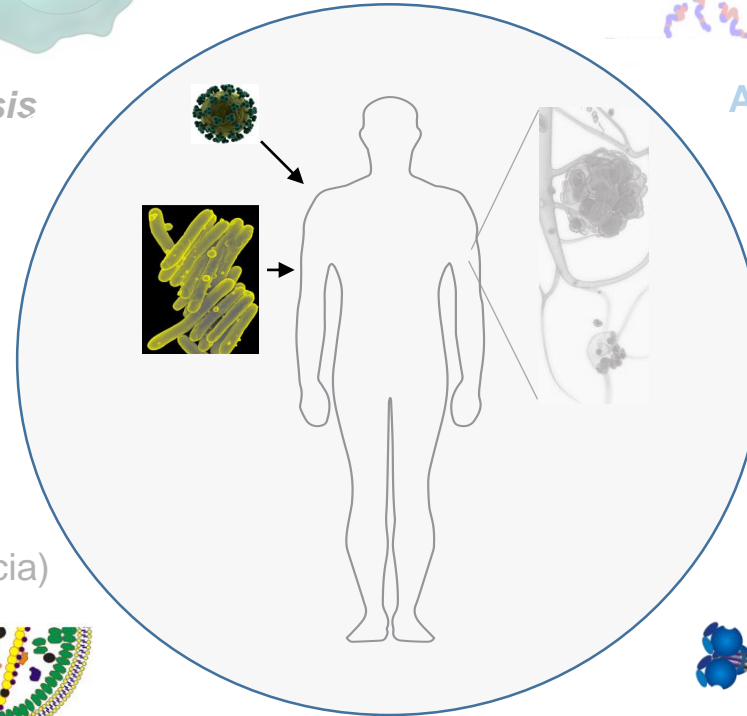
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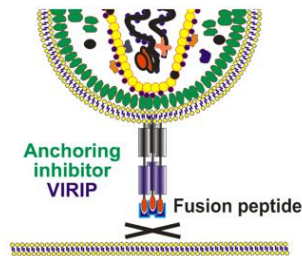
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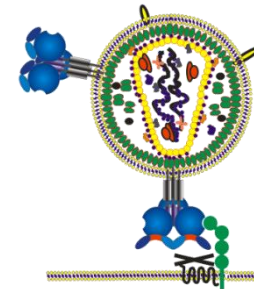
A03: Amyloid peptides
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Effective in HIV-infected people



A05: Inhibitors of viral fusion peptides
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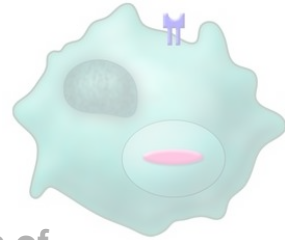


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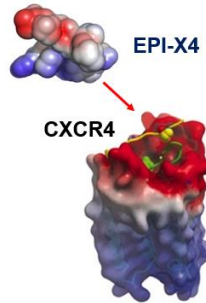
GPR15 ligand



A: Infection

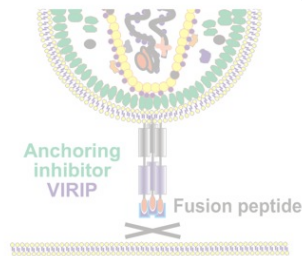


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(Michaelis, Stenger)

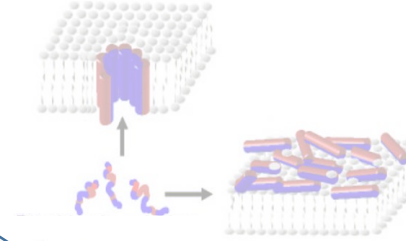


~3.200-fold activity increase

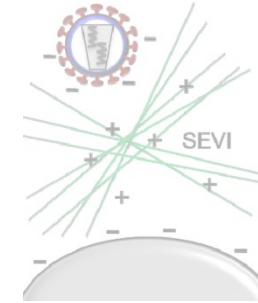
A06: Function of EPI-X4
(Klein, Münch, Sanchez-Garcia)



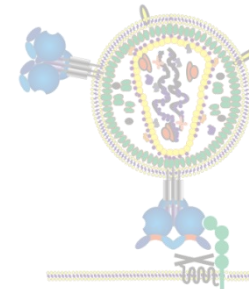
A05: Inhibitors of viral fusion peptides
(Kirchhoff, Weil)



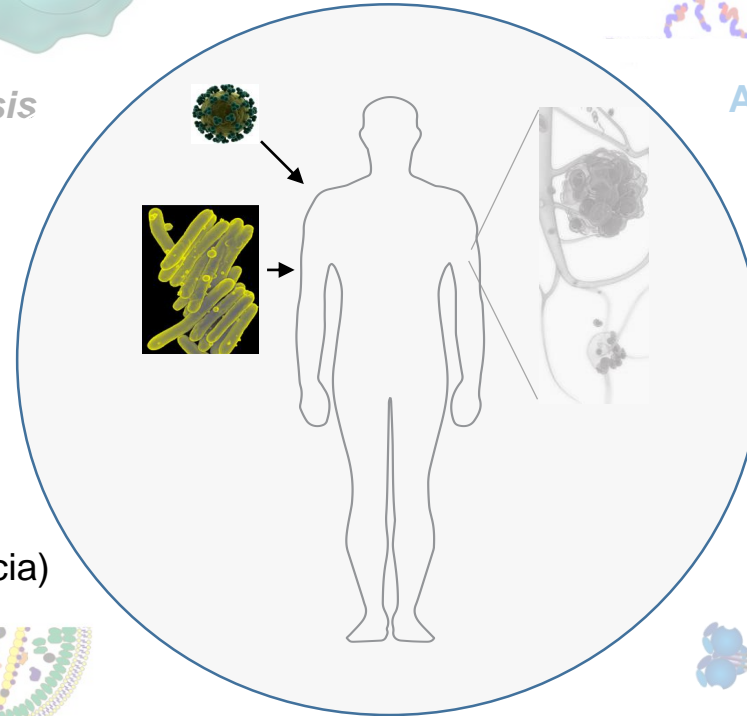
A02: Antimicrobial peptides
(Münch, Spellerberg)



A03: Amyloid peptides
(Fändrich, Münch, Walther)



A04: Novel ligands of G protein-coupled receptors
(Kirchhoff)

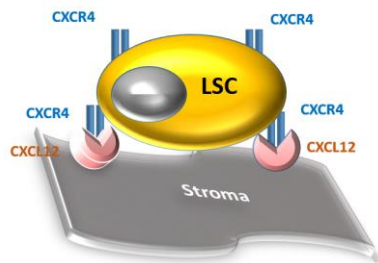




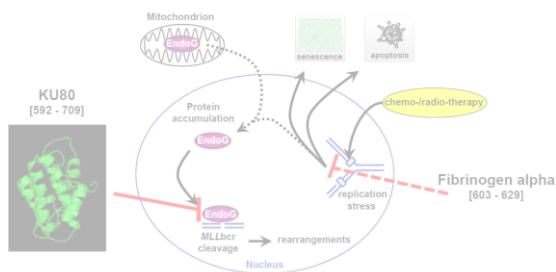
B: Cancer



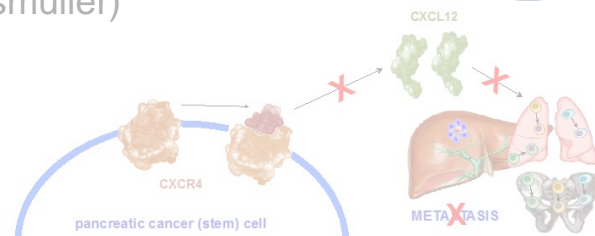
Leukemic stem cell (LSC) – niche crosstalk



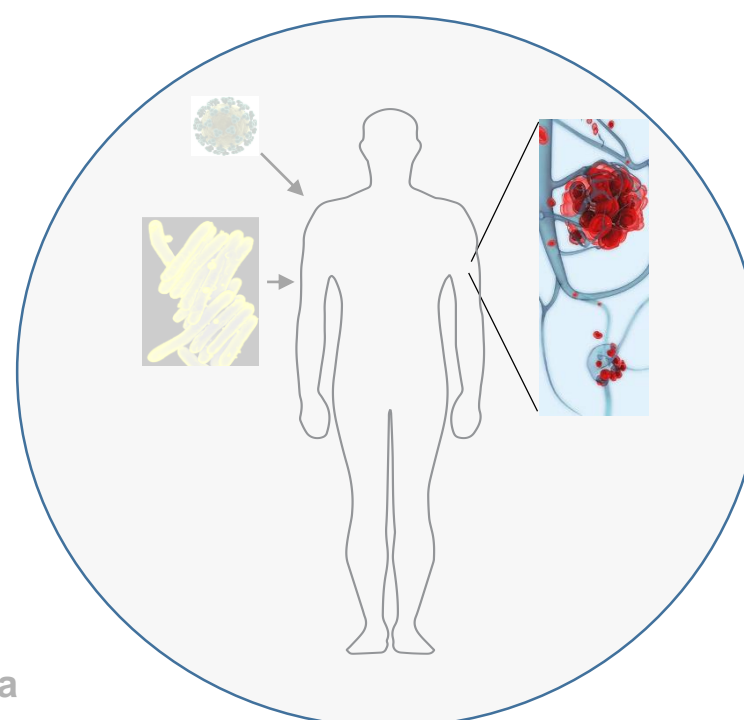
B01: CXCR4 antagonists in acute myeloid leukemia (Buske)



B05: Peptides against therapy-induced leukemia (Gebhardt, Wiesmüller)

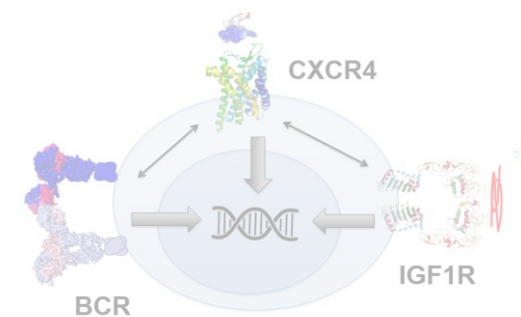


B04: CXCR4 signaling in pancreatic cancer (Hermann)



<http://hematopoiesis.info>

B02: Peptides in hematopoiesis (Geiger)



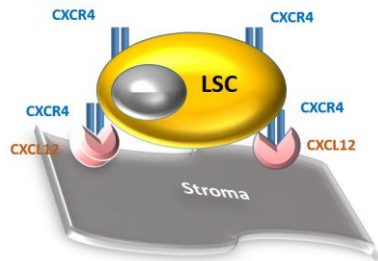
B03: Peptidic inhibitors of chronic lymphocytic leukemia (Jumaa, Übelhart)



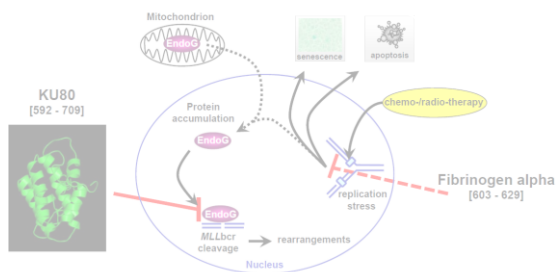
B: Cancer



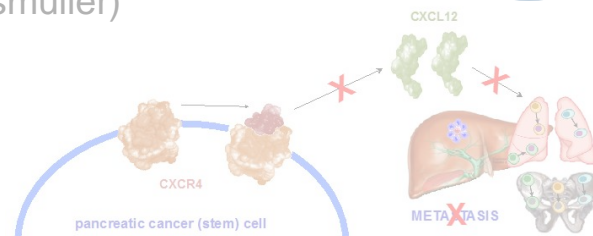
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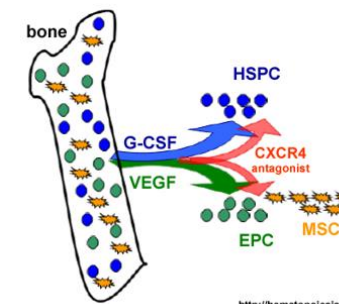
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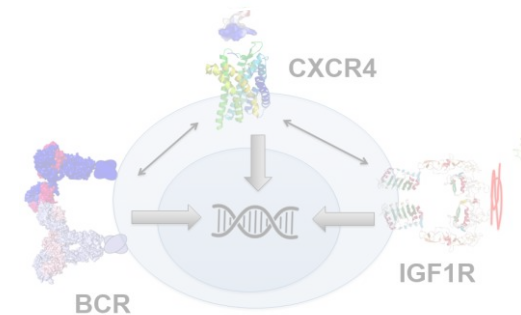


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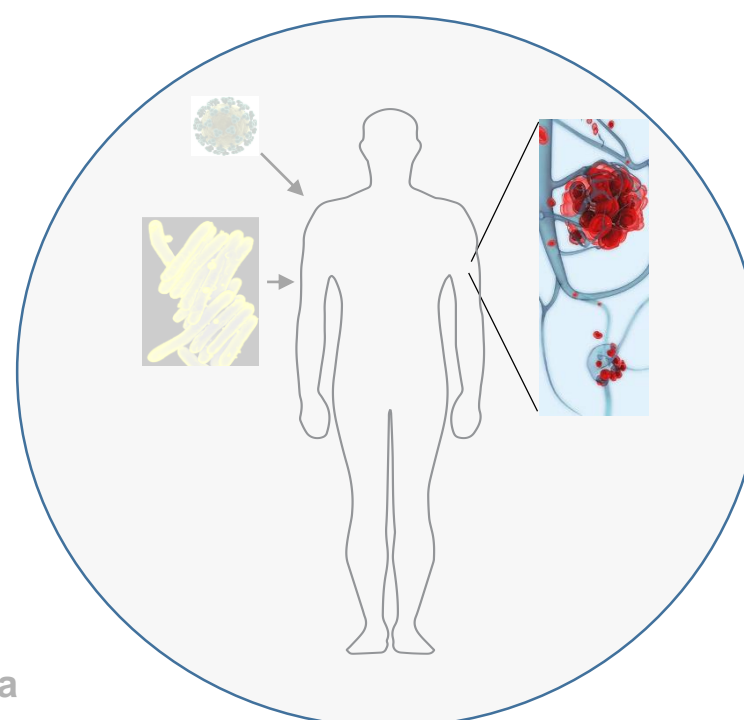


<http://hematopoiesis.info>

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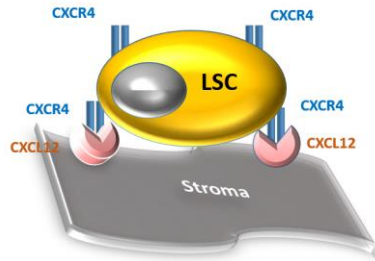




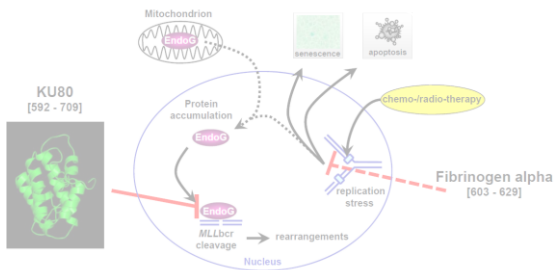
B: Cancer



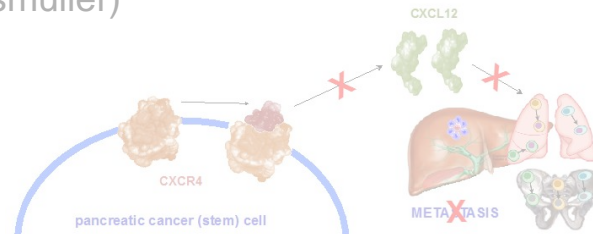
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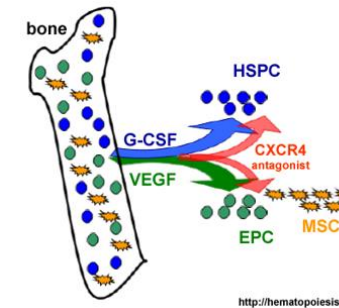
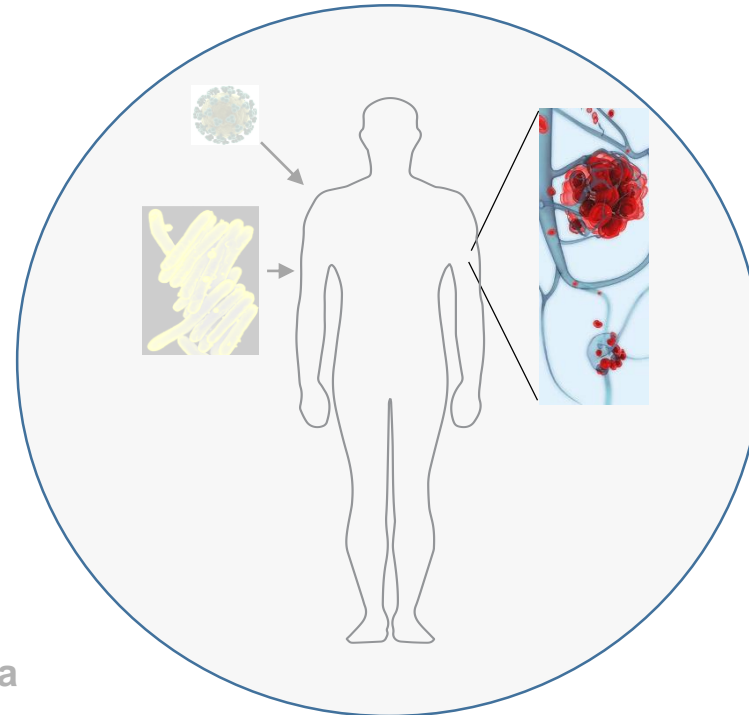
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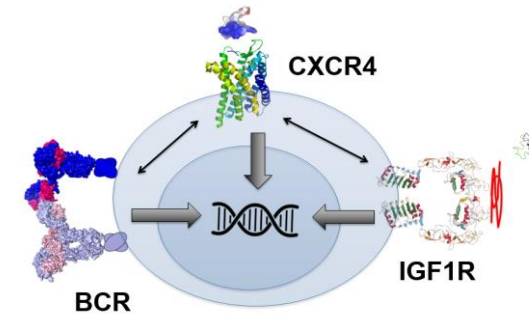
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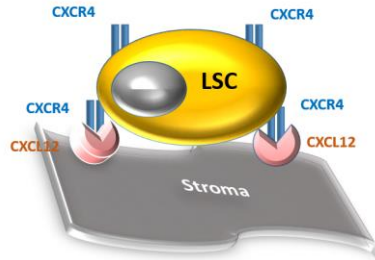


B: Cancer

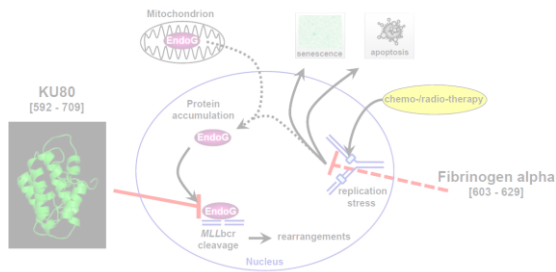


Inhibition of AML growth & engraftment

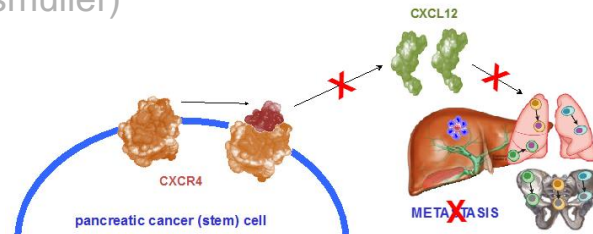
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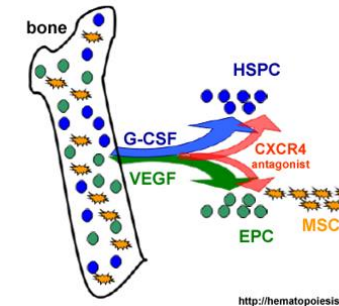


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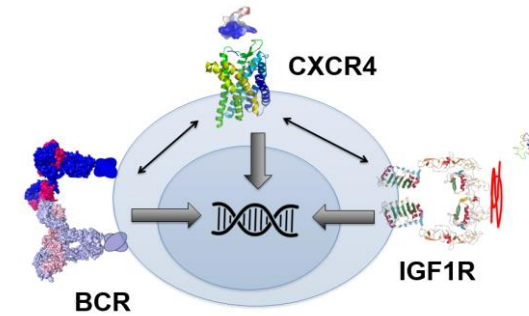


B04: CXCR4 signaling in pancreatic cancer (Hermann)

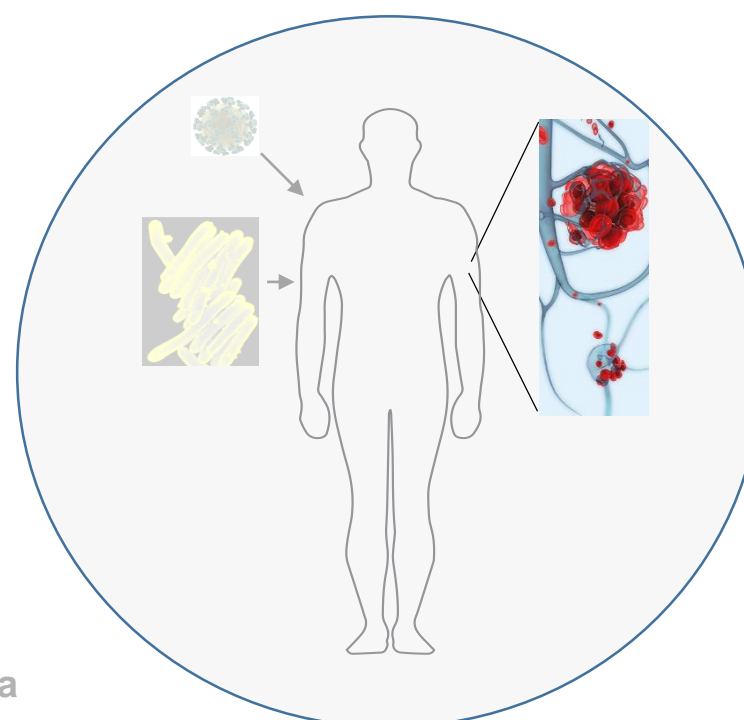
EPI-X4 blocks metastasis



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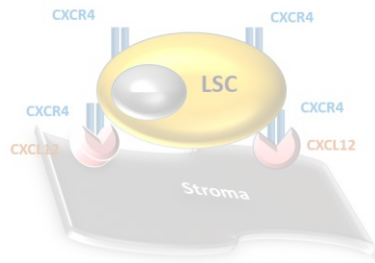




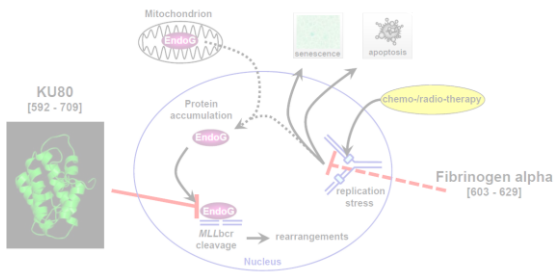
B: Cancer



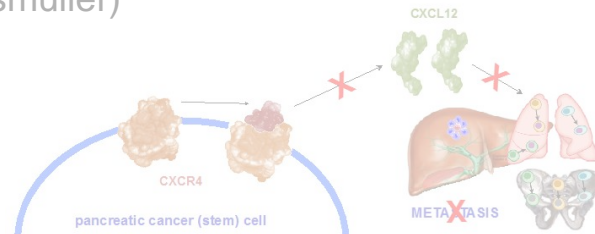
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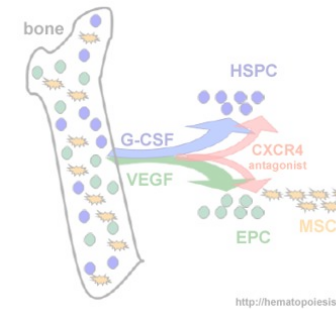
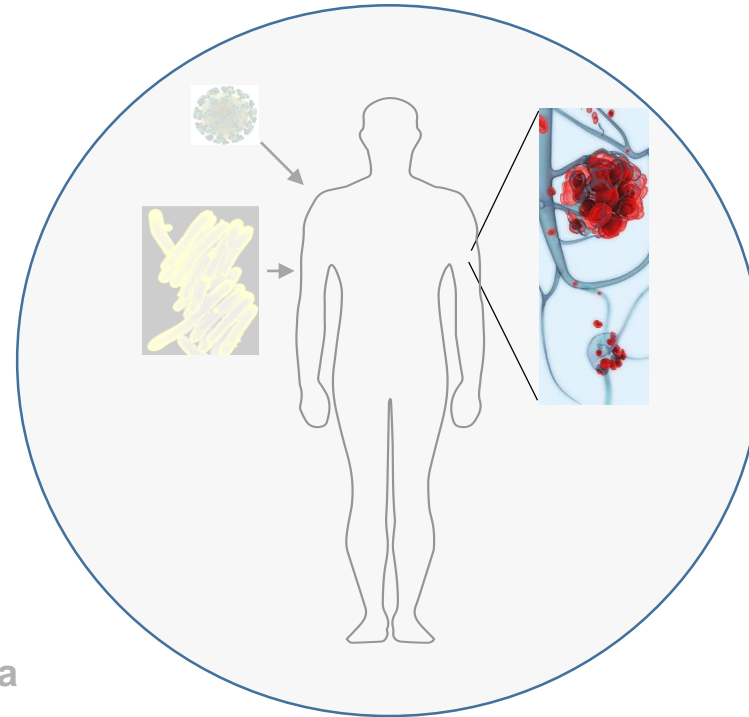
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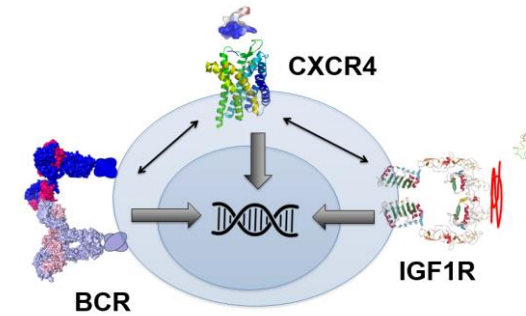
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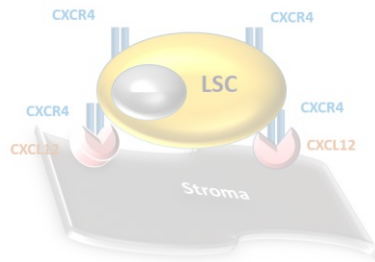
Hits against Insulin-like growth factor 1



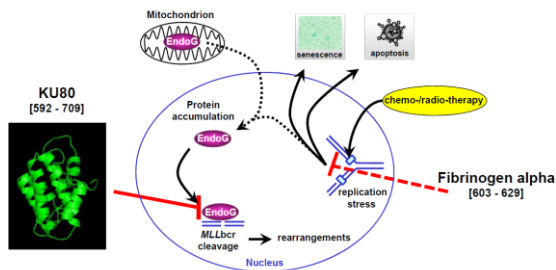
B: Cancer



Leukemic stem cell (LSC) – niche crosstalk

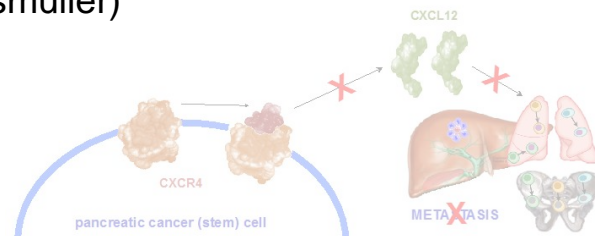


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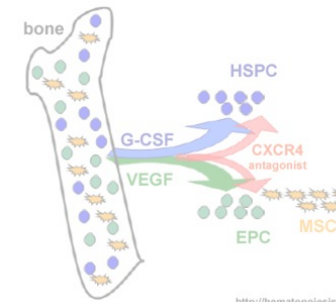


B05: Peptides against therapy-induced leukemia (Gebhardt, Wiesmüller)

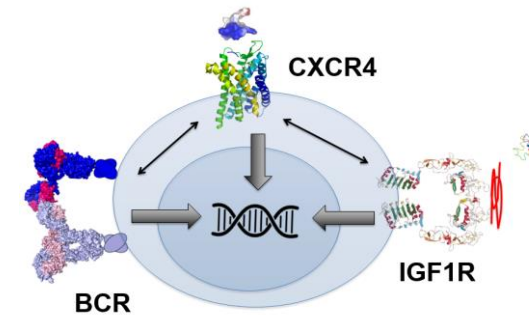
Inhibitors of DNA rearrangements



B04: CXCR4 signaling in pancreatic cancer (Hermann)



B02: Peptides in hematopoiesis (Geiger)

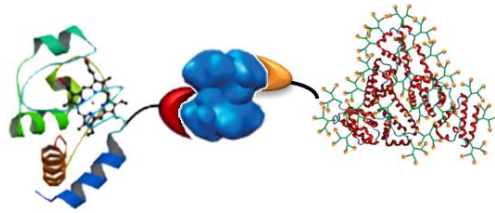


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Hits against Insulin-like growth factor 1



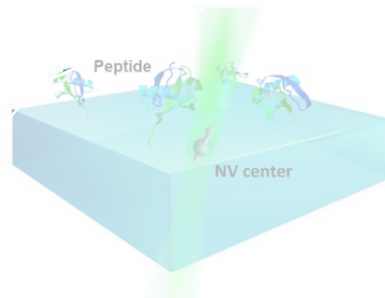
C: Optimization & novel technologies



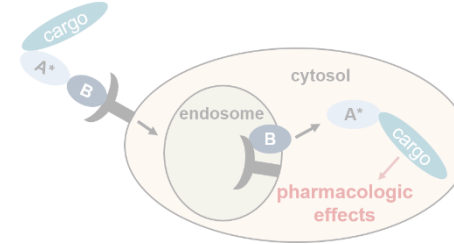
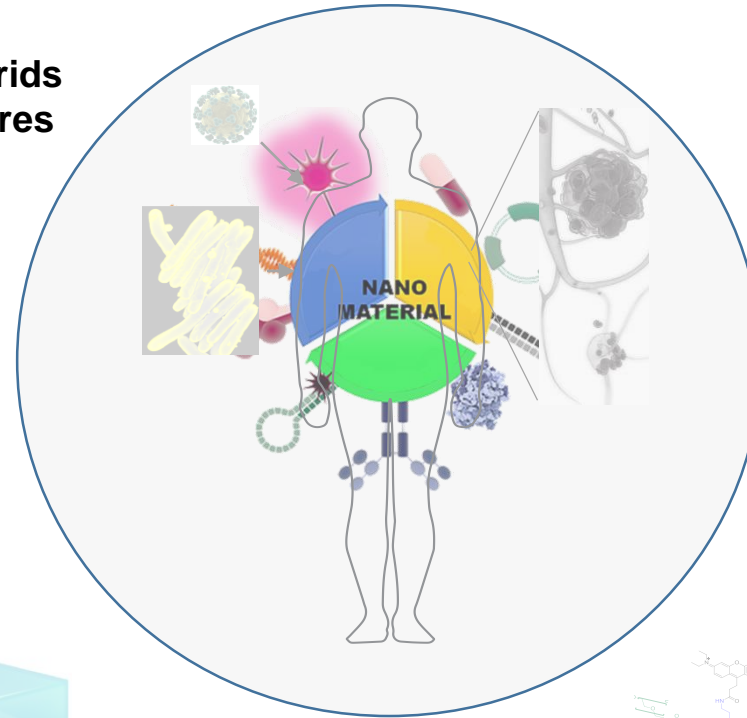
C01: Peptide biohybrids with improved features
(Otto, Weil)



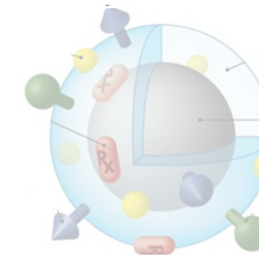
C06: Hyperpolarized peptide-coated nanodiamonds for MRI
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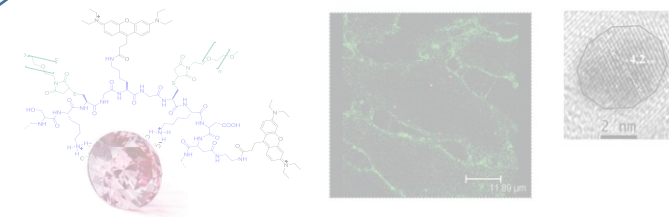
C05: Probing peptide structures with diamond sensors
(Jelezko, Plenio, Sinner)



C02: Cell-type selective transporters
(Barth, Michaelis)



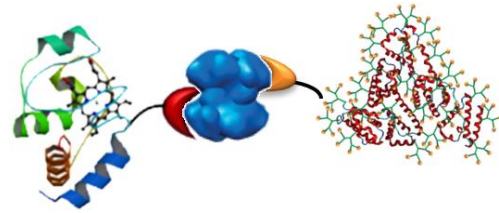
C03: Mesoporous silica particles for transport & release
(Lindén)



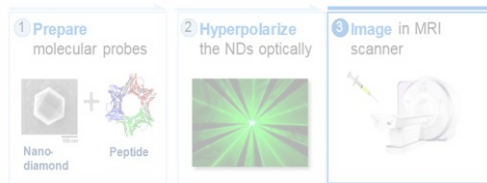
C04: Fluorescent nanodiamond transporters
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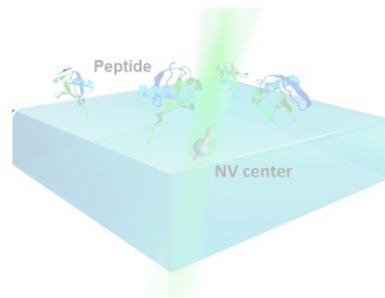
C: Optimization & novel technologies



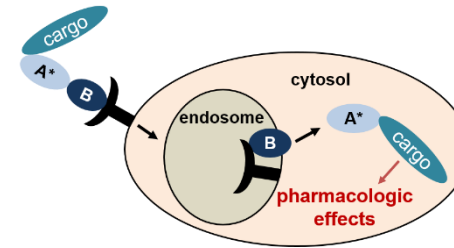
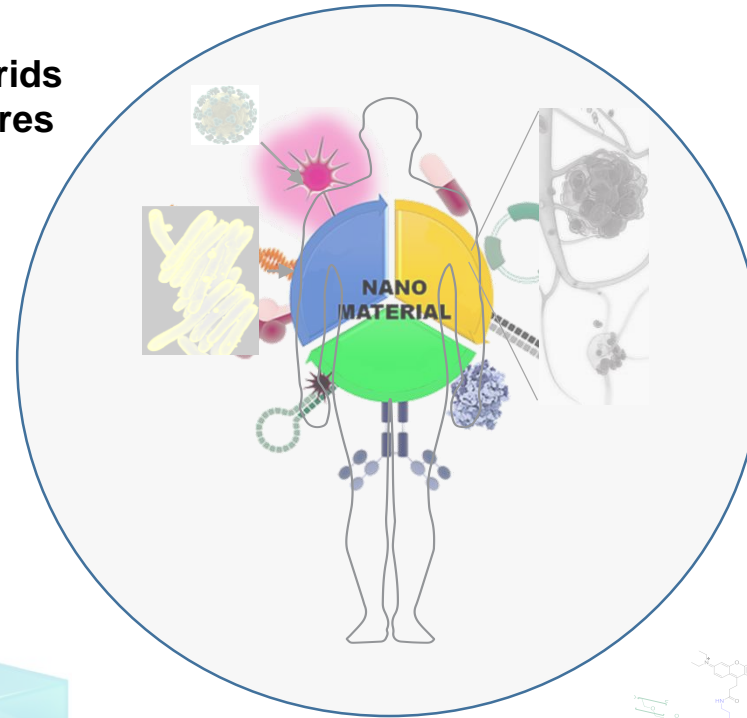
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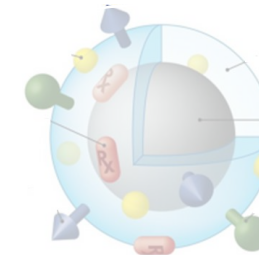
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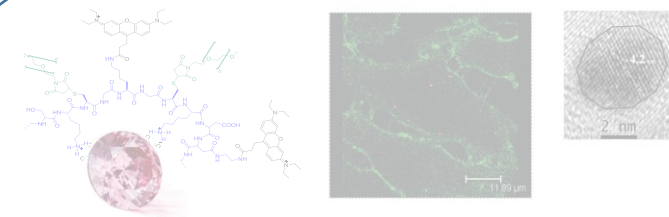
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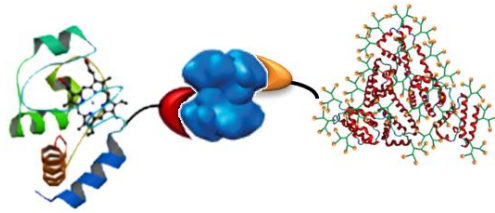
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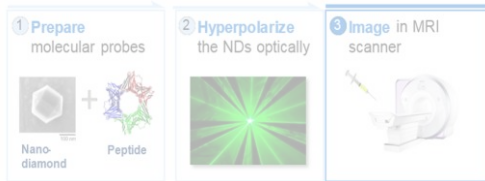
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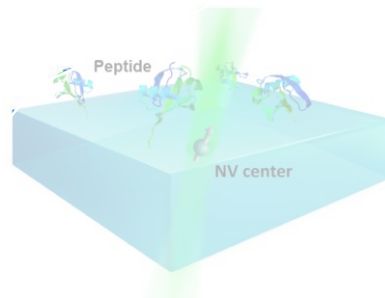
Optimization of EPI-X4



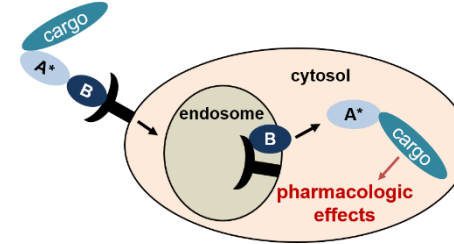
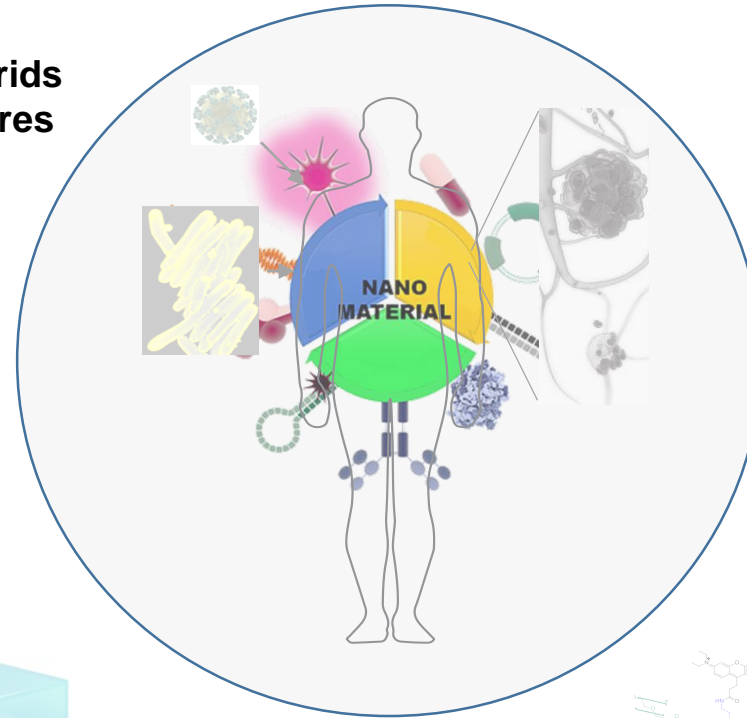
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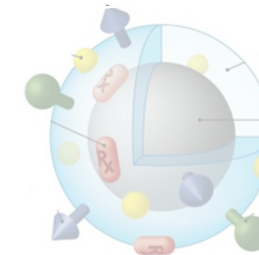
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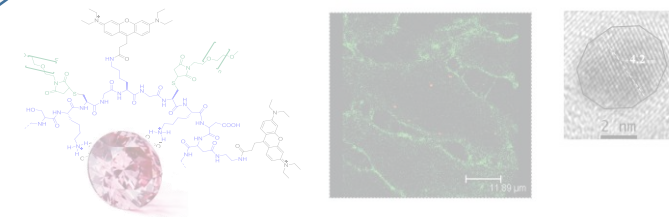
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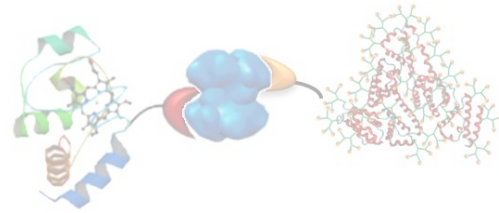
C03: Mesoporous silica particles for transport & release
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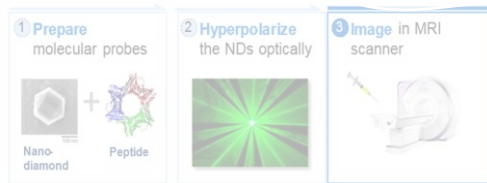
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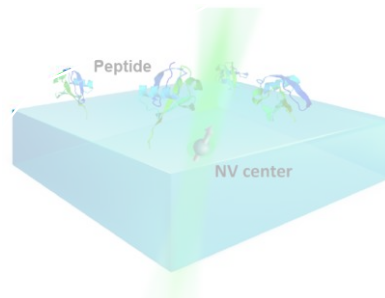
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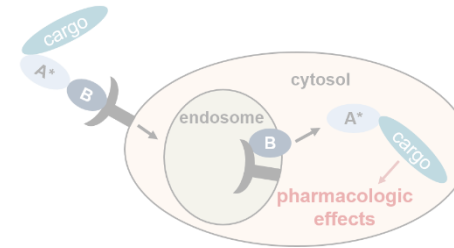
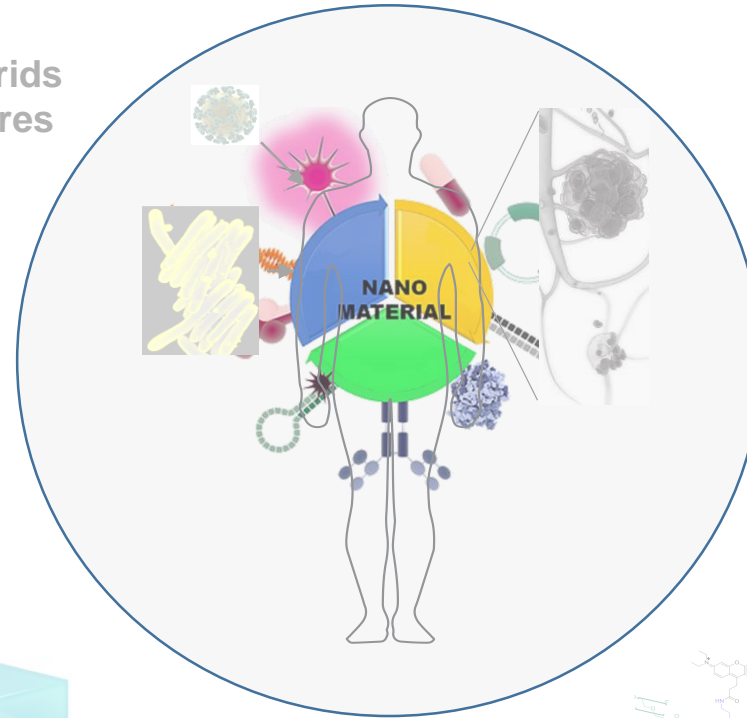
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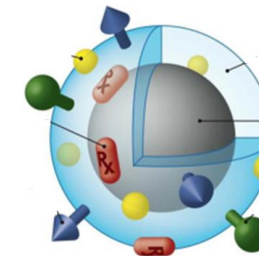
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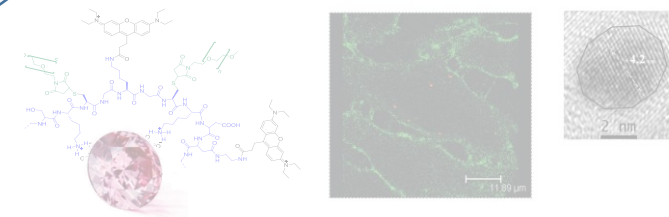
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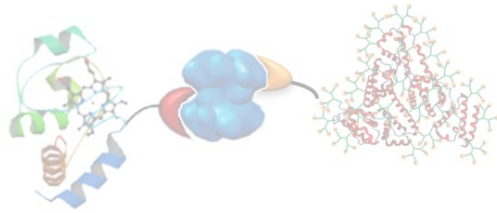
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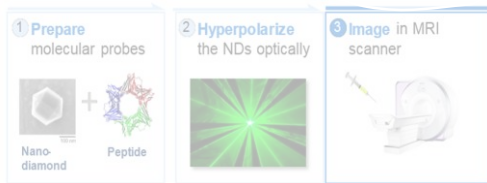
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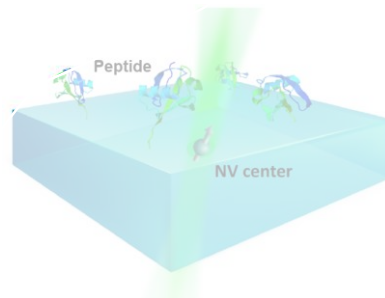
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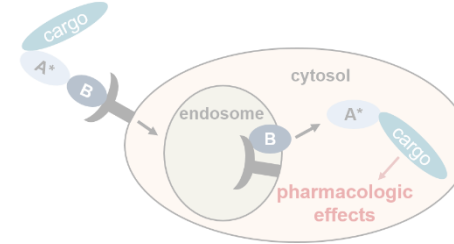
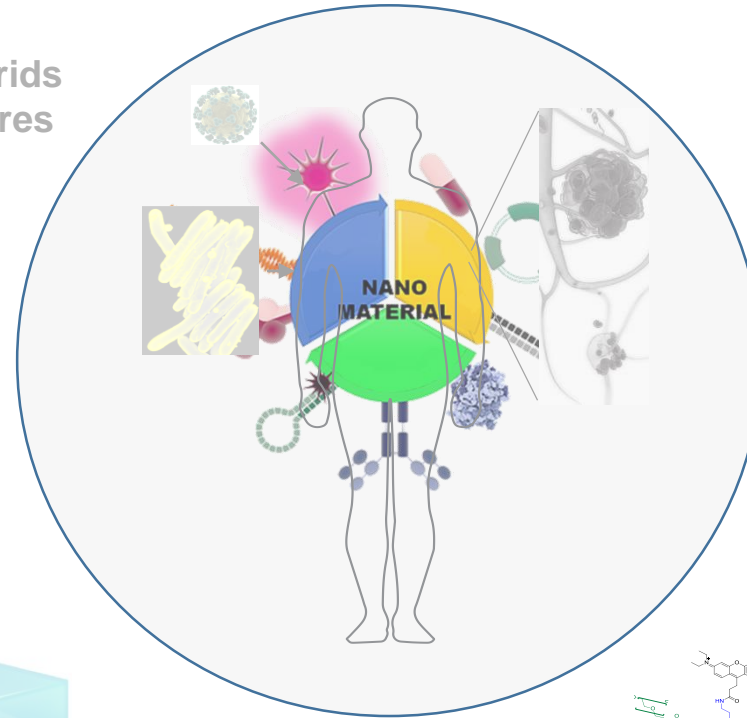
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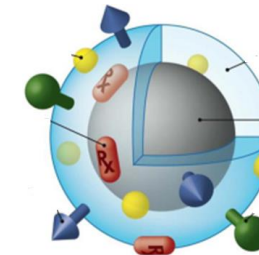
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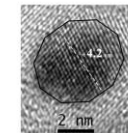
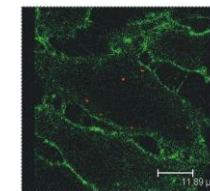
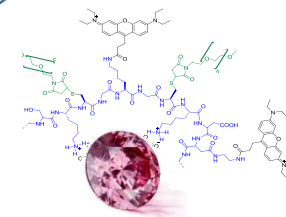


C02: Cell-type selective transporters
(Barth, Michaelis)



C03: Mesoporous silica particles for transport & release
(Lindén)

Packaging of EPI-X4 & VIR-576

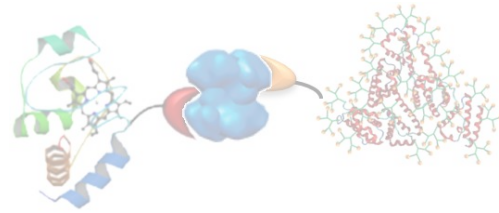


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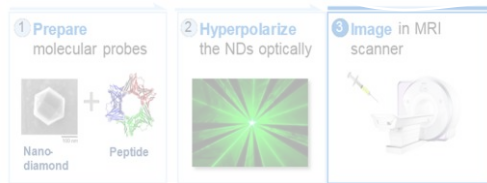
ND-based drug delivery & imaging



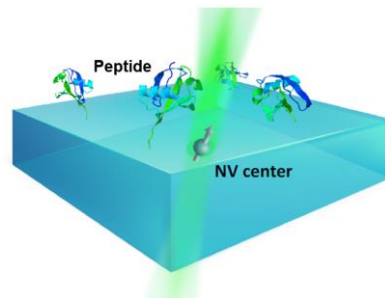
C: Optimization & novel technologies



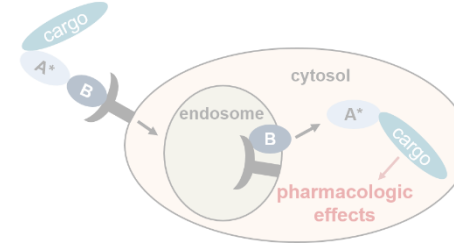
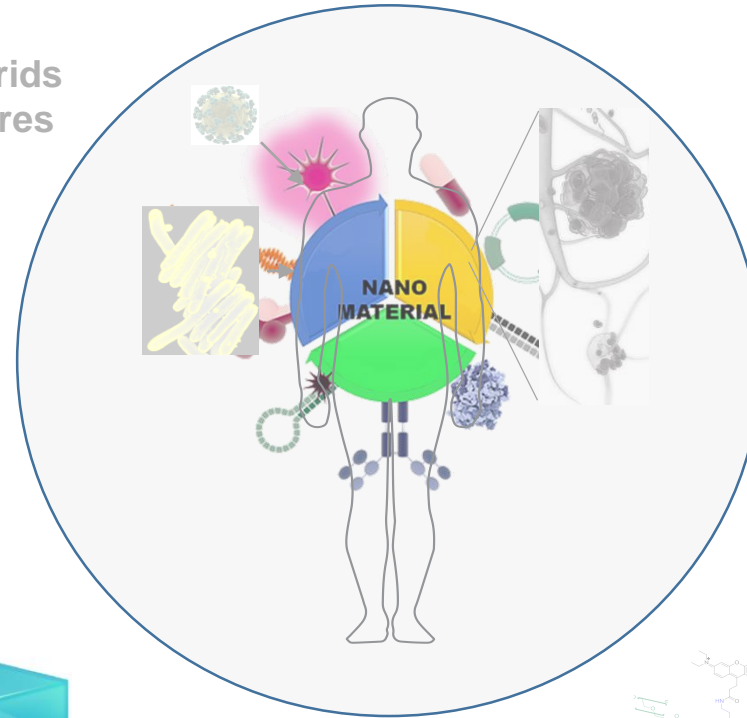
C01: Peptide biohybrids with improved features
(Otto, Weil)



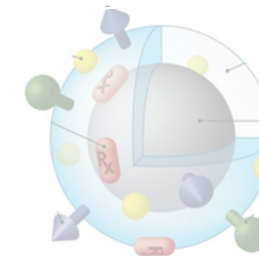
C06: Hyperpolarized peptide-coated nanodiamonds for MRI
(Buske, Jelezko, Plenio)



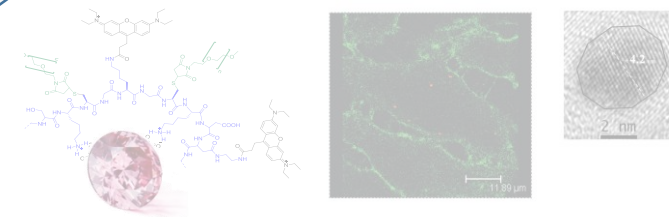
C05: Probing peptide structures with diamond sensors
(Jelezko, Plenio, Sinner)



C02: Cell-type selective transporters
(Barth, Michaelis)



C03: Mesoporous silica particles for transport & release
(Lindén)



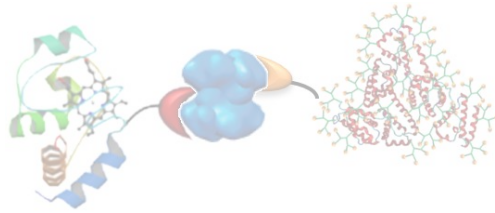
C04: Fluorescent nanodiamond transporters
(Jelezko, Wu)



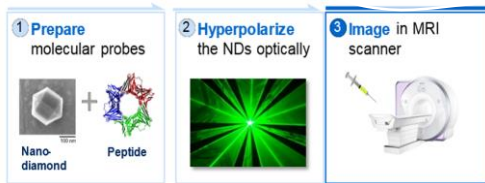
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Significant sensitivity increase

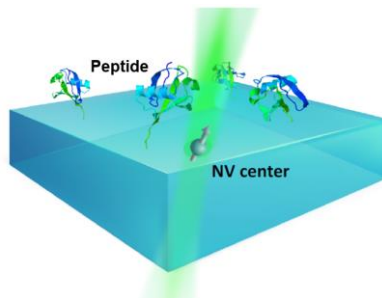


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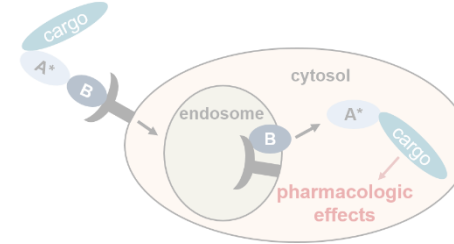
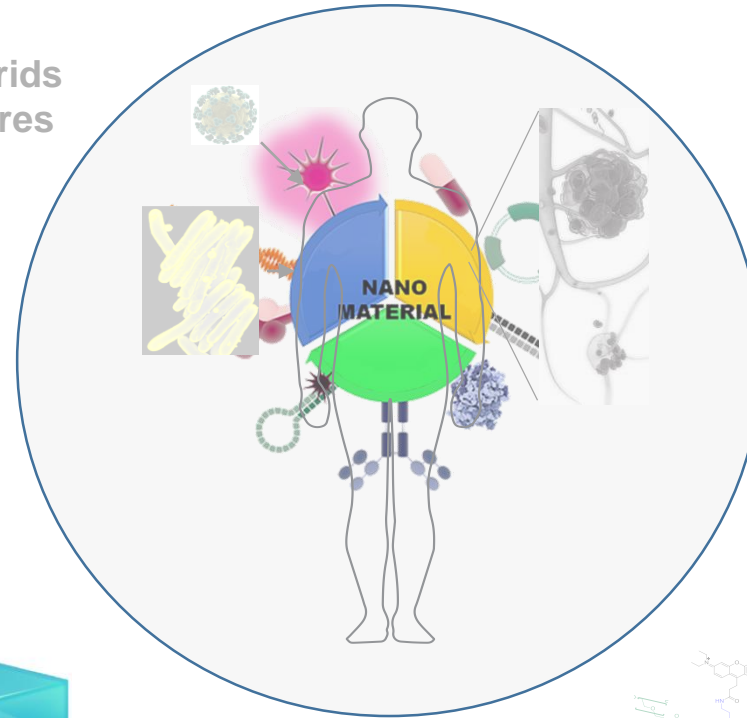


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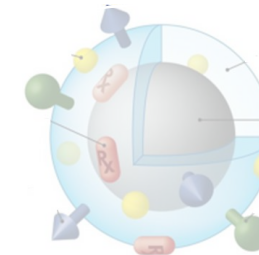
Peptide receptor interactions unraveled



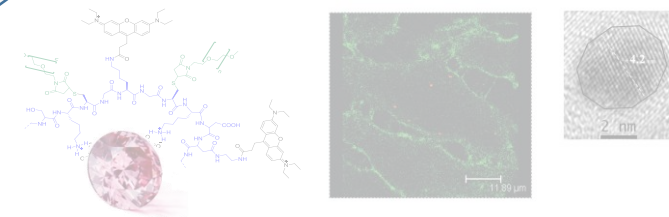
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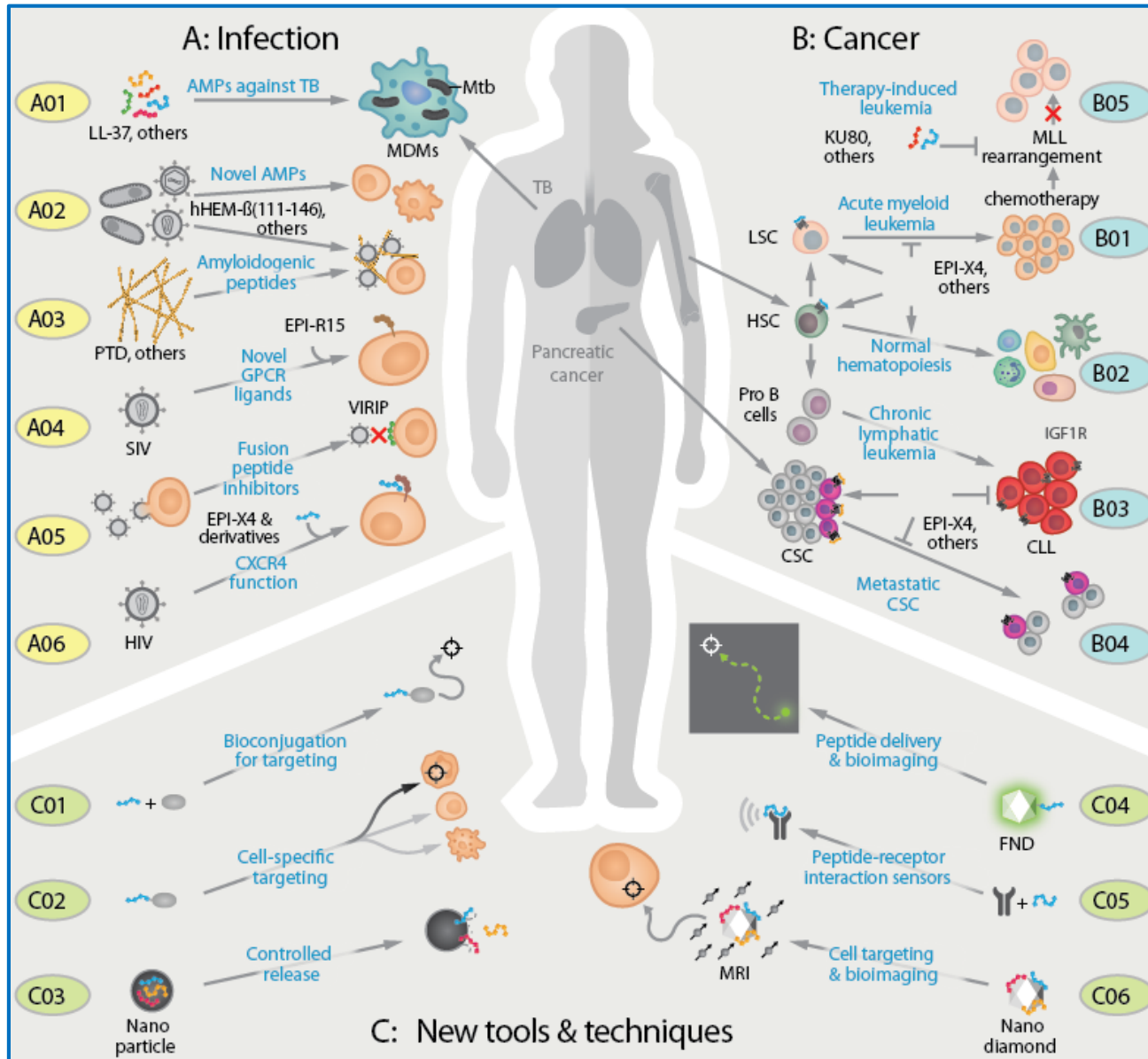
C03: Mesoporous silica particles for transport & release
(Lindén)



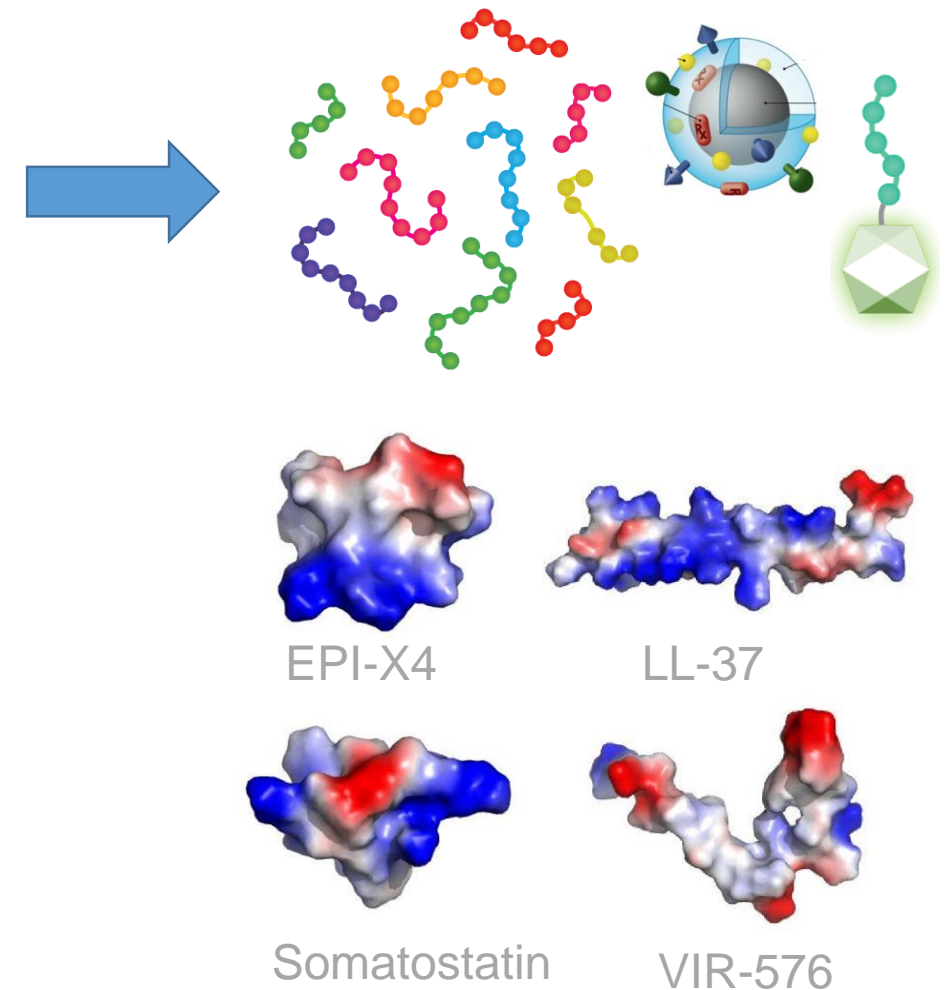
C04: Fluorescent nanodiamond transporters
(Jelezko, Wu)



Areas A-C: novel and/or optimized peptides



Candidate peptides





Z02: animal models and *in vivo* imaging



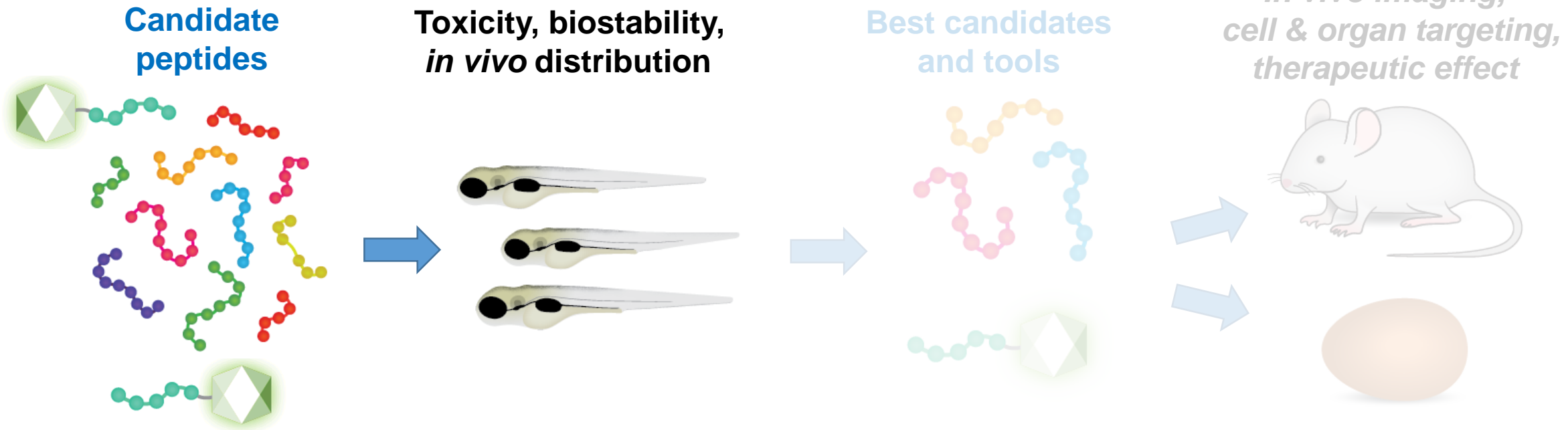
Gilbert Weidinger
Biochemistry



Ambros Beer
Nuclear medicine



Volker Rasche
Internal medicine II





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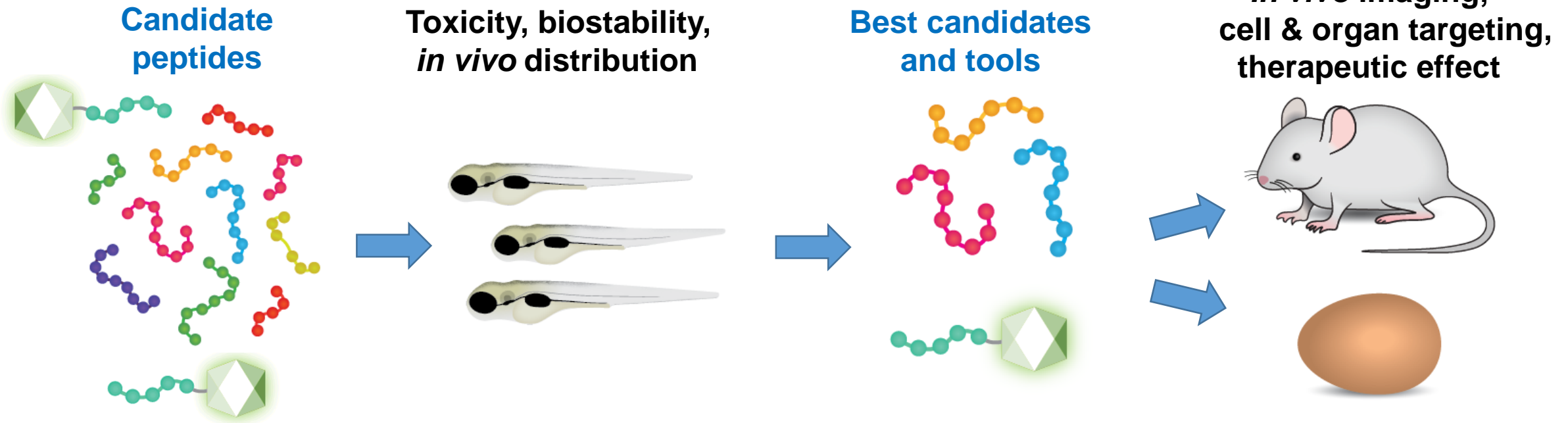
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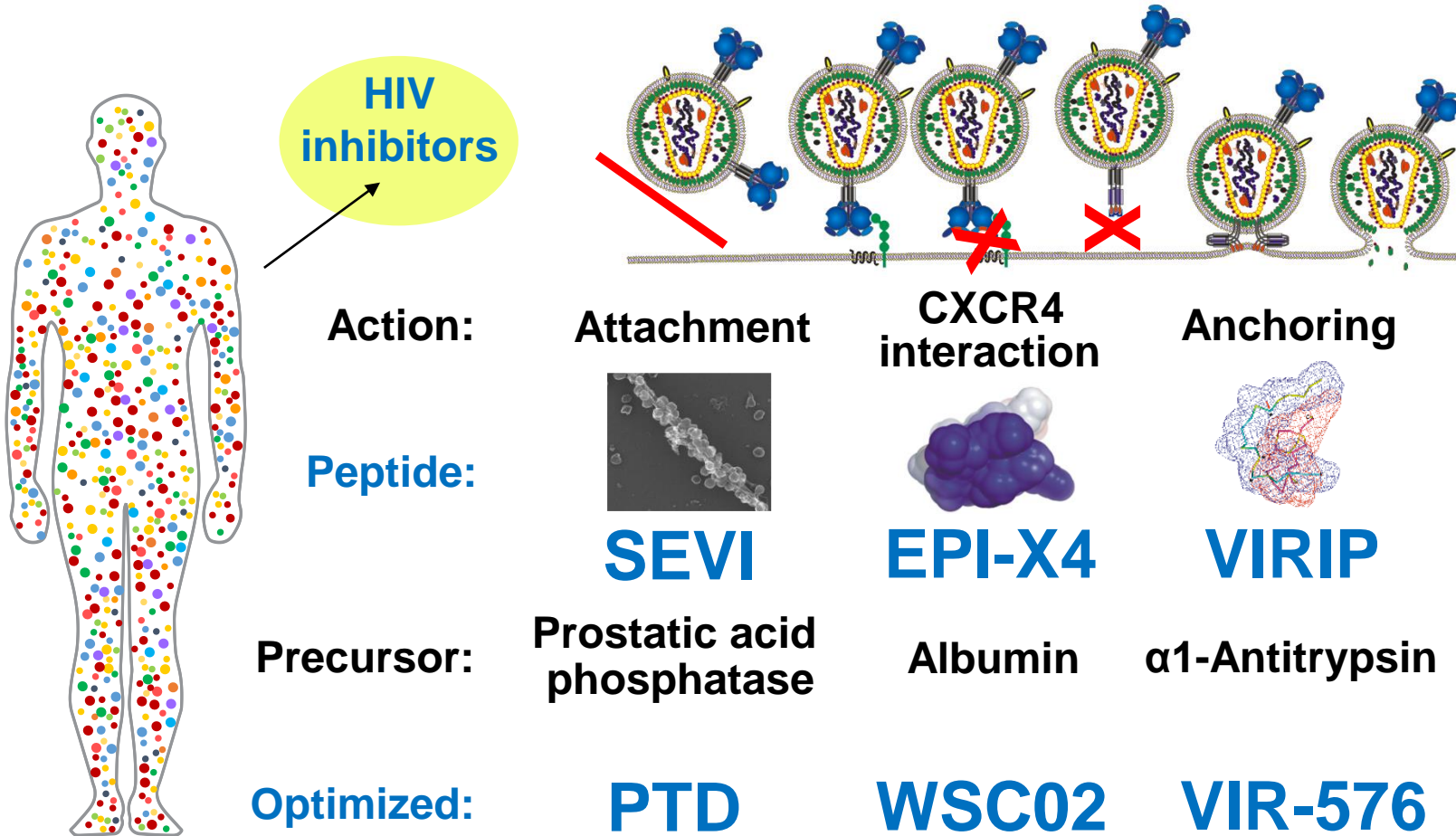




Proof of concept



Novel bioactive agents, striking mechanisms



Anal Biochem. 2015

Bone Marrow Transplant. 2016

Cell 2007a,b

Cell Host & Microbe 2011

Cell Reports 2015

Chembiochem. 2015

J. Biol. Chem. 2010

J Leukoc Biol. 2016

J. Virol. 2009, 2012, 2014

Nature 2011

Nat. Rev. Microb. 2014

Nat. Nanotech. 2013

Nat. Com. 2014

Oncotarget 2015

Retrovirology 2010, 2013

Science TM 2010, 2014



The consortium

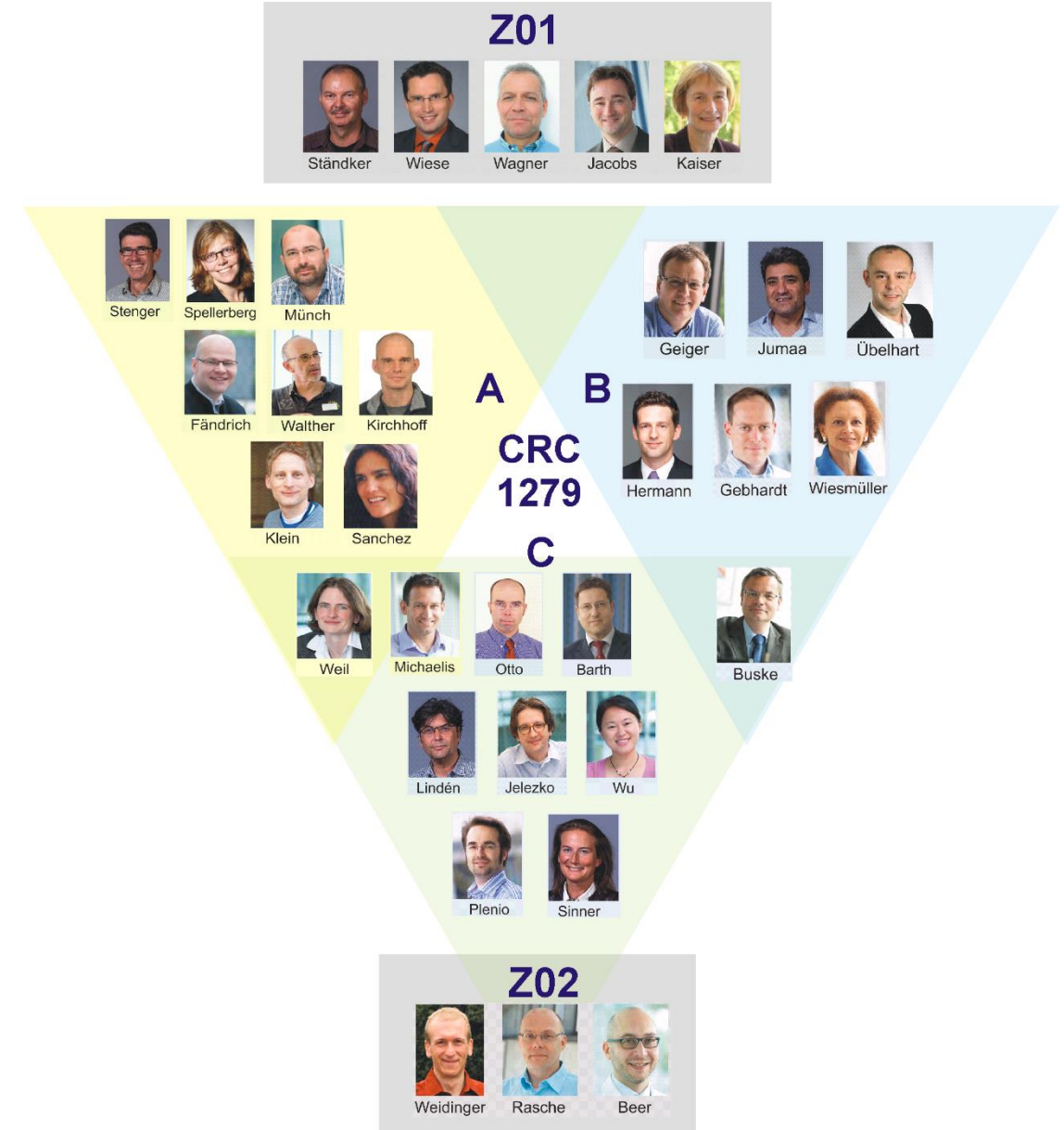


- **Scientific excellence**

- High impact publications
(Cell, Nature, Science since 2013)
- Competitive grants
(ERC, Leibniz)

- **Highly interdisciplinary**

- Shared grants and publications
- Many interdisciplinary teams
- Common initiatives

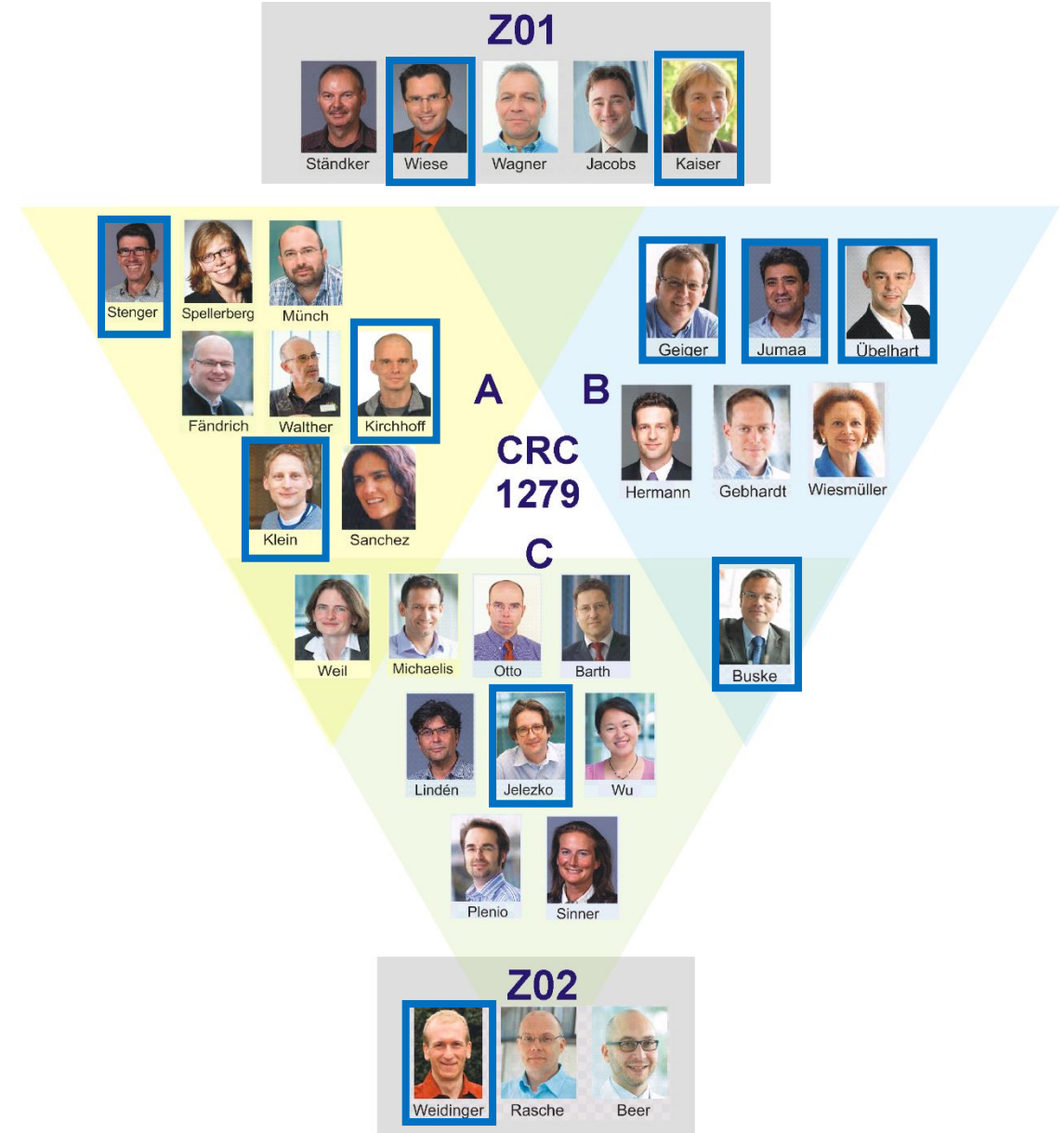




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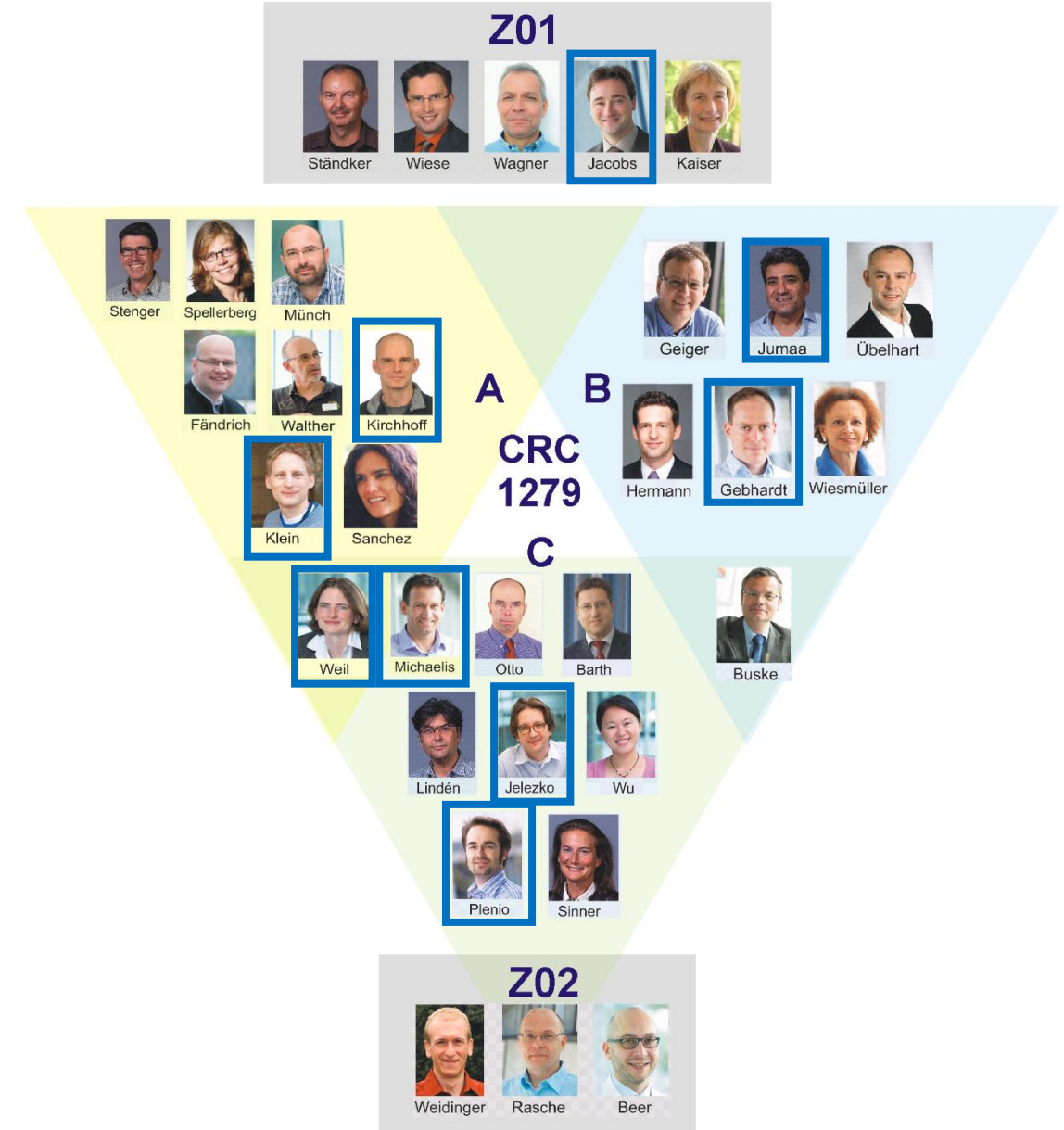
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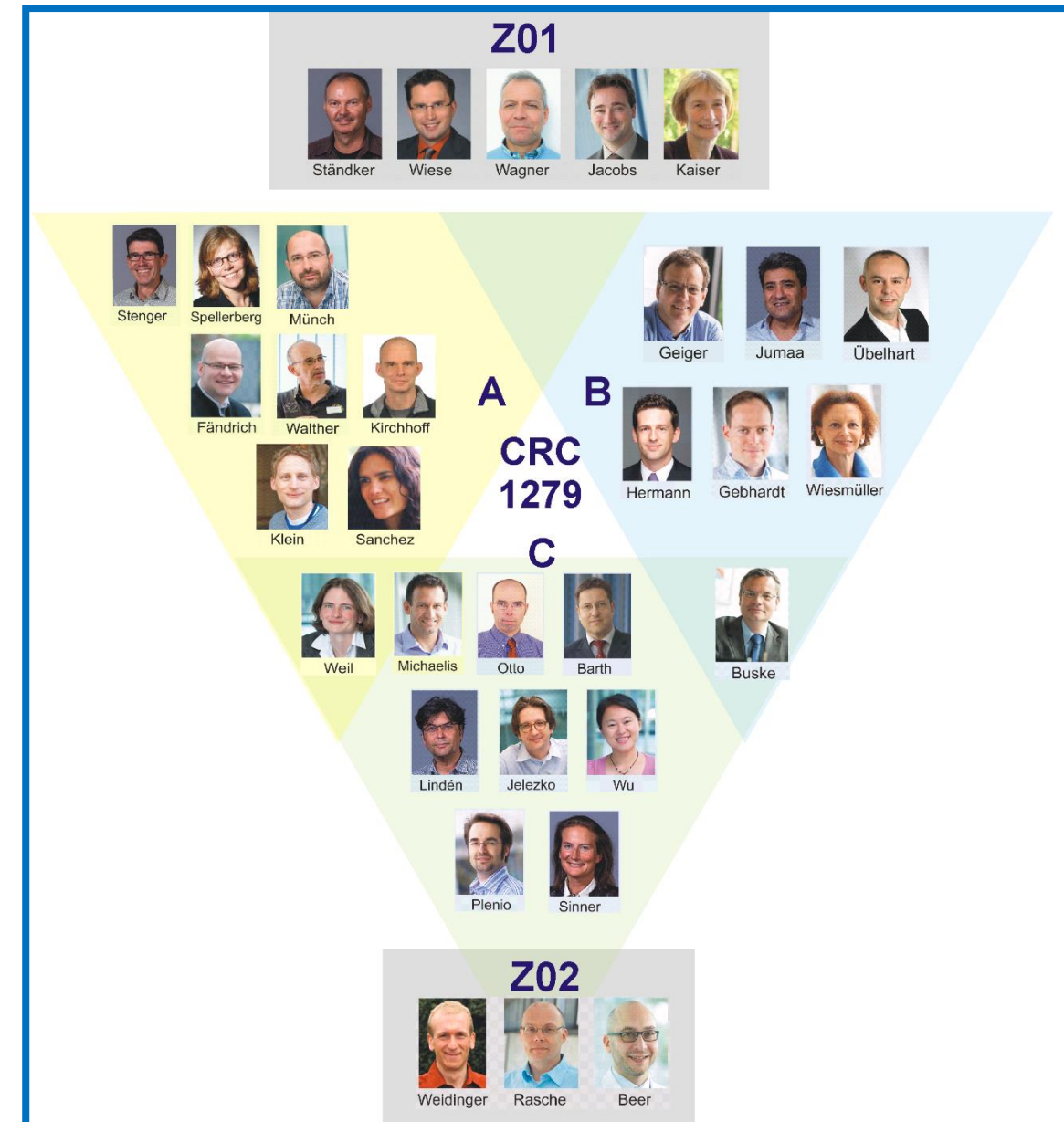




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Research structure



2013: Ulm Center for Peptide Pharmaceuticals (U-PEP; Weil, Münch, Rosenau, Kirchhoff)



- Generation of peptide libraries
- Discovery of bioactive peptides
- Peptide purification & synthesis



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- Diamond quantum-sensing
- Application quantum biology
- Biomedical research



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Building costs ~27 million €
Six million € from Ulm University



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Appointments in the last 7 years

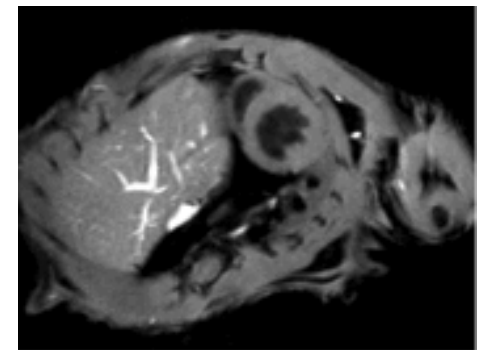
- **Prof. Dr. Frank Kirchhoff** (W3mL, year of appointment 2009);
Director of the Institute of Molecular Virology
- **Prof. Dr. Christian Buske** (W3mL, year of appointment 2009);
Director of the Institute for Experimental Cancer Research
- **Prof. Dr. Martin Plenio** (W3mL, year of appointment 2009);
Director of the Institute of Theoretical Physics
- **Prof. Dr. Jan Münch** (W3oL, year of appointment 2010);
Institute for Molecular Virology
- **Prof. Dr. Tanja Weil** (W3mL, year of appointment 2010);
Director of the Institute of Organic Chemistry III until 2016
Director of the Max-Planck Institute for Polymer Research in Mainz
and honorary professor at Ulm University since 2016)
- **Prof. Dr. Mika Lindén** (W3mL, year of appointment 2010);
Director of the Institute of Inorganic Chemistry II
- **Prof. Dr. Fedor Jelezko** (W3mL, year of appointment 2011);
Director of the Institute of Quantum Optics
- **Prof. Dr. Jens Michaelis** (W3mL, year of appointment 2011);
Director of the Institute of Biophysics
- **Prof. Dr. Timo Jacob** (W3mL, year of appointment 2011)
Institute of Electrochemistry
- **Prof. Dr. Marcus Fändrich** (W3mL, year of appointment 2012);
Director of the Institute of Protein Biochemistry
- **Prof. Dr. Gilbert Weidinger** (W3oL, year of appointment 2012);
Research Professor, Institute of Biochemistry and Molecular Biology
- **Prof. Dr. Christof Gebhardt** (W3oL, year of appointment 2013)
Institute of Biophysics
- **Prof. Dr. Hartmut Geiger** (W3mL, year of appointment 2013);
Director of the Institute of Molecular Medicine
- **Prof. Dr. Hassan Jumaa** (W3mL, year of appointment 2013)
Director of the Institute of Immunology
- **Prof. Dr. Ambros Beer** (W3mL, year of appointment 2014)
Director of the Department of Nuclear Medicine



Infrastructure



- **Core Functional Peptidomics** (just founded, head: L. Ständker, Z01)
- **Center for Quantum Biosciences (Z^{QB})** (Plenio, Jelezko, Weil & Kirchhoff)
- **Core Unit Mass Spectrometry & Proteomics** (since 2014; head: S. Wiese, Z01)
- **Ulm Center for Pep. Pharmaceuticals (U-PEP)** (Münch, Ständker, Weil & Kirchhoff)
- **Electron microscopy facility** (head: P. Walther, A03)
- **Sub-Angstrom Low-Voltage Electron Microscopy (SALVE; head: U. Kaiser, Z01)**
- **Small Animal Imaging** (head: V. Rasche, Z02)
- **Genome Centre** (head: Ch. Buske, B01, C06)
- **Cell sorting facility** (head: Ch. Buske, B01, C06)
- **Animal facility, including transgenic mouse facility**
- **Core Facility Confocal and Multi-photon Microscopy**
- **Bioinformatics and Systems Biology** (since 2016; head: H. Kestler)
- **GMP-grade cell expansion and processing facility** (head: H. Schrezenmeier)

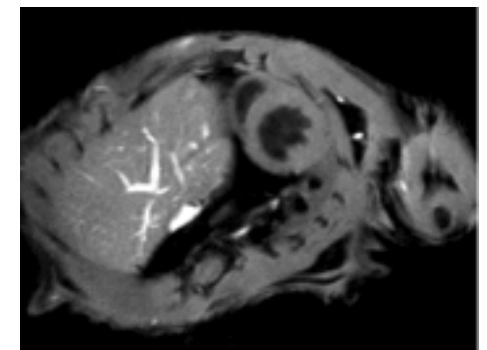




Infrastructure

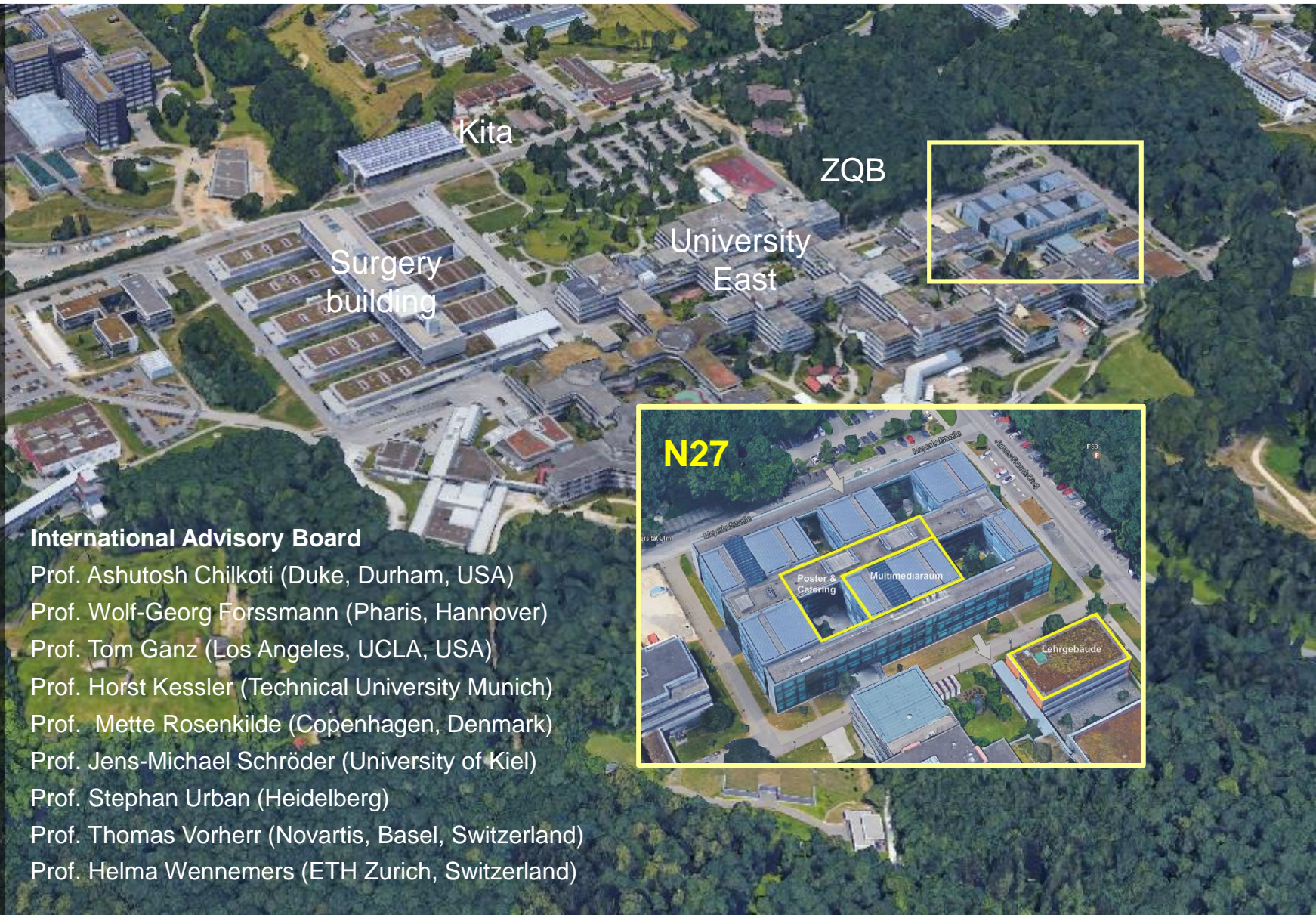


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Location



Medical Faculty

- Core Unit Mass Spectrometry and Proteomics (CUMP)
- Core Unit Functional Peptidomics (CFP)
- Department of Internal Medicine I
- Department of Internal Medicine II
- Department of Neurology
- Department of Nuclear Medicine
- Department of Obstetrics and Gynecology
- Institute for Biochemistry and Molecular Biology
- Institute for Immunology
- Institute of Medical Microbiology and Hygiene
- Institute for Experimental Cancer Research – CCC Ulm
- Institute of Molecular Virology
- Institute of Pathology-Laboratory for Neuropathology
- Institute of Pharmacology and Toxicology

Faculty of Natural Sciences

- Institute for Biochemistry
- Institute for Quantum Optics
- Institute of Advanced Energy Related Nanomaterials
- Institute of Biophysics
- Institute of Electrochemistry
- Institute of Inorganic Chemistry II
- Institute of Organic Chemistry II & Advanced Materials
- Institute of Protein Biochemistry
- Institute of Theoretical Physics

Central Institutions of Ulm University

- Central Facility of Electron Microscopy
- Institute of Molecular Medicine

International Advisory Board

- Prof. Ashutosh Chilkoti (Duke, Durham, USA)
- Prof. Wolf-Georg Forssmann (Pharis, Hannover)
- Prof. Tom Ganz (Los Angeles, UCLA, USA)
- Prof. Horst Kessler (Technical University Munich)
- Prof. Mette Rosenkilde (Copenhagen, Denmark)
- Prof. Jens-Michael Schröder (University of Kiel)
- Prof. Stephan Urban (Heidelberg)
- Prof. Thomas Vorherr (Novartis, Basel, Switzerland)
- Prof. Helma Wennemers (ETH Zurich, Switzerland)





Additional external expertise



Tanja Weil (Mainz/Ulm)
Bioconjugation & others

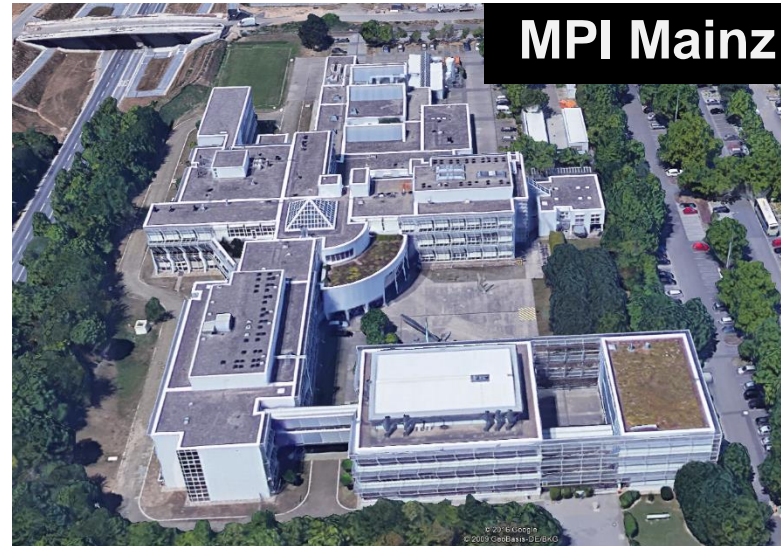
Yuzhou Wu (Mainz)
Nanodiamonds

Manfred Wagner (Mainz)
NMR structures

Florian Klein (Cologne)
Humanized mice

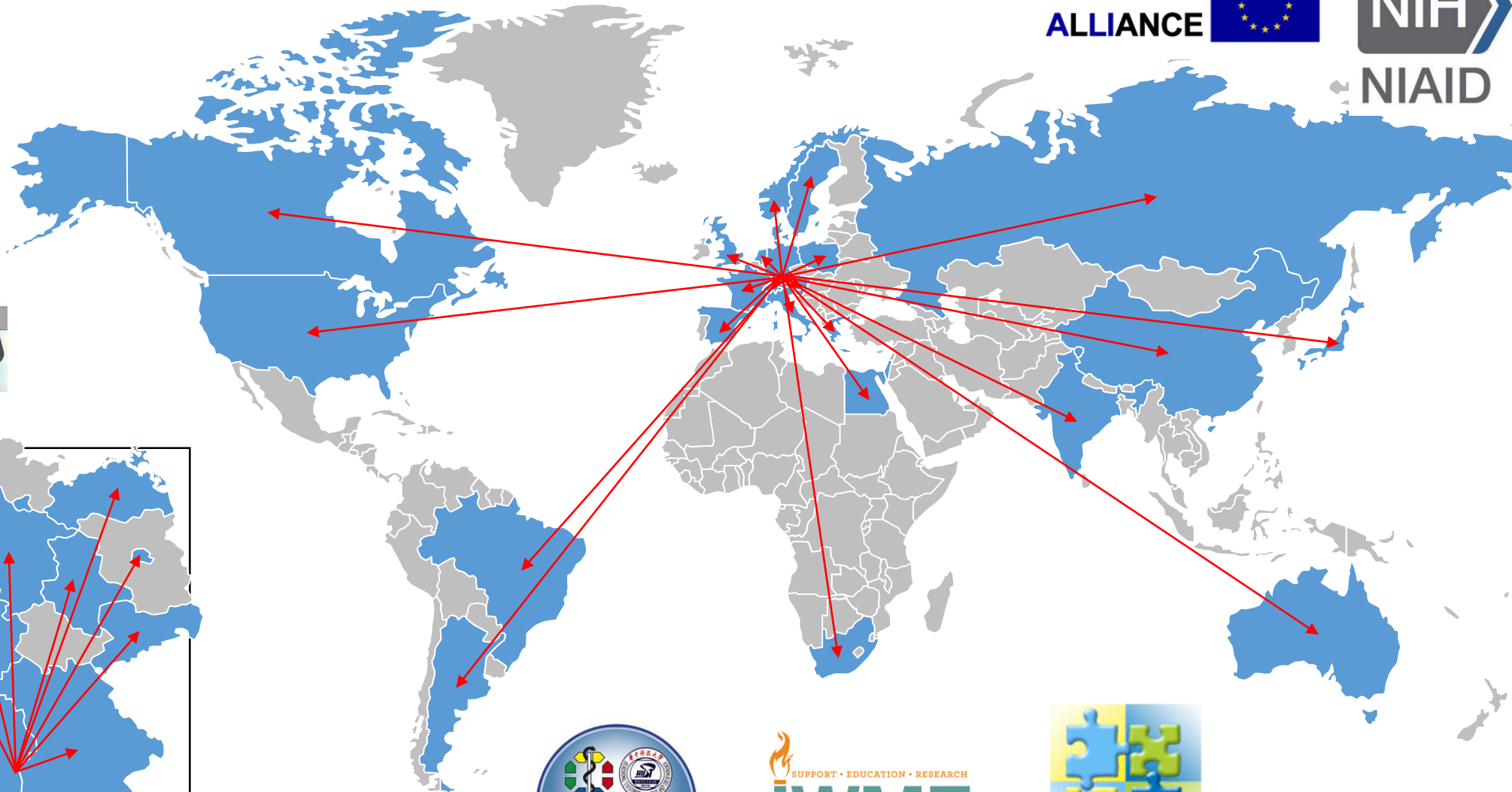
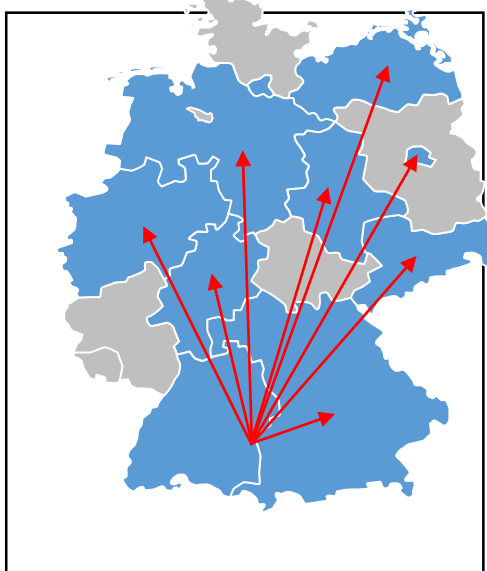
Elsa Sanchez-Garcia
(Mülheim a.d. Ruhr)
Molecular Modelling

Eva Sinner (Vienna)
Artificial membranes





Cooperations





Career support within CRC 1279



Seven young investigators

Z01



**Sebastian
Wiese**

A06



**Florian
Klein**

A06



**Elsa
Sanchez
Garcia**

B03



**Rudolf
Übelhart**

B04



**Patrick
Hermann**

B05



**Christof
Gebhardt**

C04



**Yuzhou
Wu**

Positions:

7 PostDocs

25 PhD students

2 Clinical scientists

92% for young investigators



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UUlM and the state of BW has many programmes to support young and/or female scientists

- “Baustein” program (e.g. Übelhart, B03; Herrman, B04)
- “Gerok” positions (two within CRC 1279 one financed by Med. Faculty)
- Hertha Nathorff Program (advancement of female scientists)
- Margarete von Wrangell Habilitation Program (for female scientists)



Christina Stürzel
(A05, C03)



Dominik Hotter
(A04)



Career support within CRC 1279



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Yuzhou
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International Graduate School in Molecular Medicine Ulm (IGradU)



International Graduate School
in Molecular Medicine Ulm

- More than 200 students
- Interdisciplinary
- Many PIs are already supervising
- Track: Cancer (C. Buske)
- Track: Host-pathogen interactions (F. Kirchhoff)





Career support within CRC 1279



Seven young investigators

Z01



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Wiese

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Florian
Klein

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C04



Yuzhou
Wu

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Specific actions of CRC 1279

Interdisciplinarity, networking & independent critical thinking

- Rotations between the three scientific research areas
- Special courses in state-of-the-art technologies
- Research stipends for international exchange
- Support by Undergraduate students “HiWis”





Gender support within CRC 1279



Excellent female scientists contribute to all research areas of the proposed CRC 1279



Z01



Ute
Kaiser

A02



Barbara
Spellerberg

A05
C01



Tanja
Weil

A06



Elsa
Sanchez
Garcia

B05



Lisa
Wiesmüller

C04



Yuzhou
Wu

C05



Eva
Sinner

Gender equality & family-friendly measures

- **Mentoring Program: to combine science and family**
- **Margarete von Wrangell Post-Doctoral Program**
- **Schlieben-Lange Program: for Female Scientists with Children**
- **Mileva Einstein-Maric-Award: 5,000 € for excellent female scientists**
- **The Medical Faculty's Intramural Support Program**
- **Child Care Centre: e.g. technical support in case of pregnancy**
- **Hertha Nathorff Program: scientific career development**
- **Holiday Care Programs: e.g. "Research Holidays" & "Science Camp"**

Supporting actions of CRC 1279

- **Funding of participations in scientific conferences**
- **Participation of the CRC at Ulm University's Girls Days**
- **Seminars on equal opportunities**
- **Funding of child care during scientific events**
- **Planning of seminars under consideration of child care schedules**
- **Special seminars e.g. in scientific writing of grants and publications**
- **Technical support for pregnant researchers**



Strengths of CRC 1279



- **Uniqueness of the approach (functional peptidomics)**
- **Highly relevant (infectious diseases & cancer)**
- **Proven feasibility (interesting agents purified & optimized)**
- **Potential (much remains to be discovered & optimized)**
- **Prerequisites (established cooperations, core facilities, U-PEP, Z^{QB})**
- **Integrates several key research areas (added benefit)**
- **Scientific excellence (evident from many awards, grants & publications)**
- **Interdisciplinarity (from quantum physics to preclinical studies)**
- **Excellent young & female investigators (strong support programmes)**