Department of Pharmaceutical and Pharmacological Sciences

KU Leuven – ON2 building

Rega Institute – MedChem division

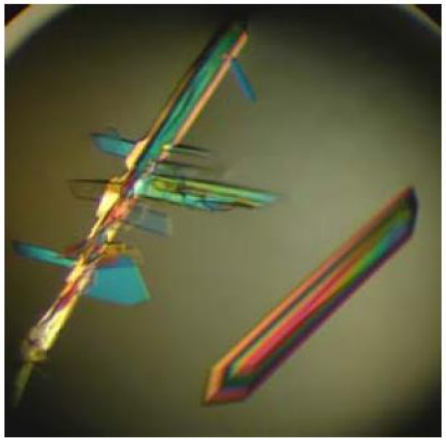
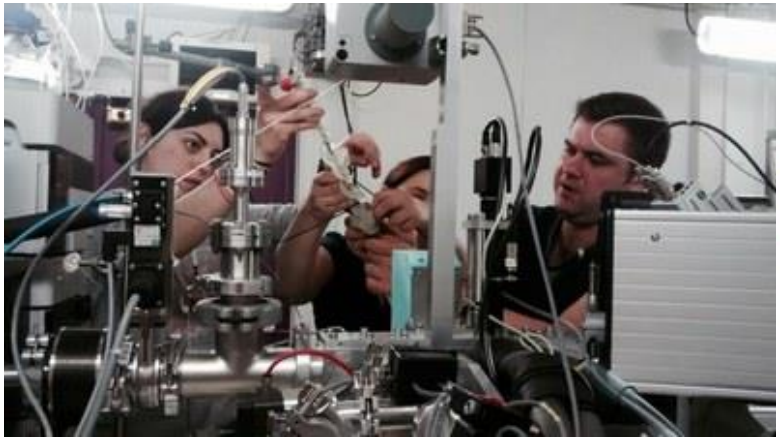
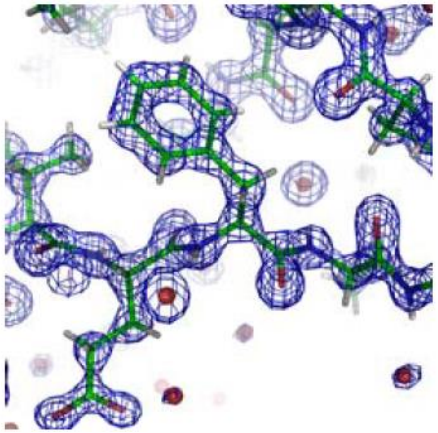
KU LEUVEN

Cloud 1 – Target Validation and Drug Discovery

target validation & drug **DISCOVERY** → **DEVELOPMENT** of therapeutics & diagnostics → drug delivery, disposition & (bio)**ANALYSIS** → clinical pharmacology & pharmaco**THERAPY**

Cell Metabolism	Prof. Myriam Baes	
Molecular Virology & Gene Therapy	Prof. Zeger Debyser 	Prof. Rik Gijsbers 
Biocrystallography	Prof. Sergei Strelkov 	
Molecular Biodiscovery	Prof. Peter de Witte 	
Toxicology & Pharmacology	Prof. Jan Tytgat 	Prof. Eva Cuypers 

Biocrystallography

Techniques:

X-ray crystallography, SAXS, macromolecular modeling and drug design, biotechnology, biochemistry, mass spectrometry, EM

Prof. Dr. S. Strelkov and Dr. S. Weeks
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stephen.weeks@kuleuven.be

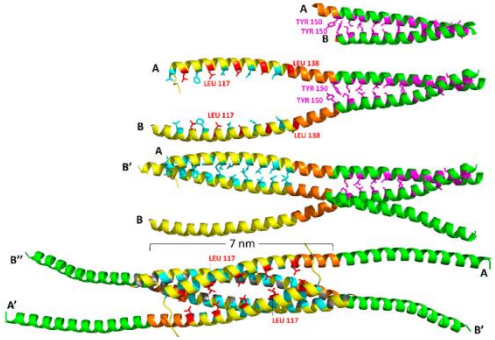
Biocrystallography (Scientific Highlights)

- **Ongoing research on cytoskeletal intermediate filaments**

Chernyatina et al (2015) Curr Opin Cell Biol. 32:65-72;

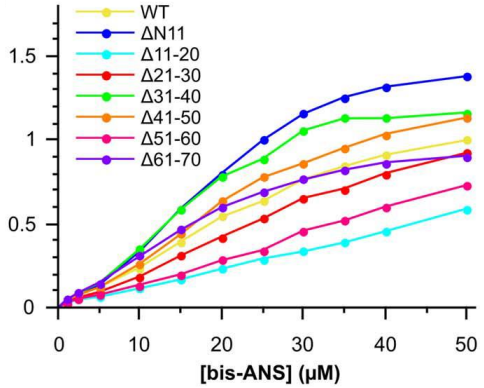
Clemen et al (2013) Acta Neuropathol. 125(1):47-75;

Chernyatina et al (2012) Proc Natl Acad Sci U S A. 109(34):13620-5.



- **Ongoing structural studies of small heat-shock proteins**

Heirbaut et al (2014) PLoS One. Aug 26;9(8):e105892.



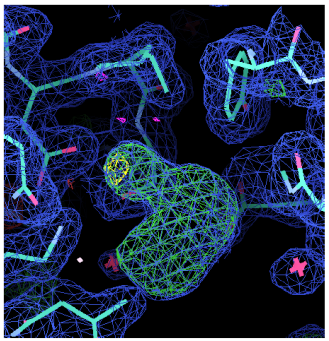
- **Past and recently started structural projects aimed at drug design -- novel antivirals and antibiotics (tRNA synthetases)**

Christ et al (2010) Nat Chem Biol. 6(6):442-8.

Zhang et al (2018) EJMECH, 148, 384-396

- **Methods development**

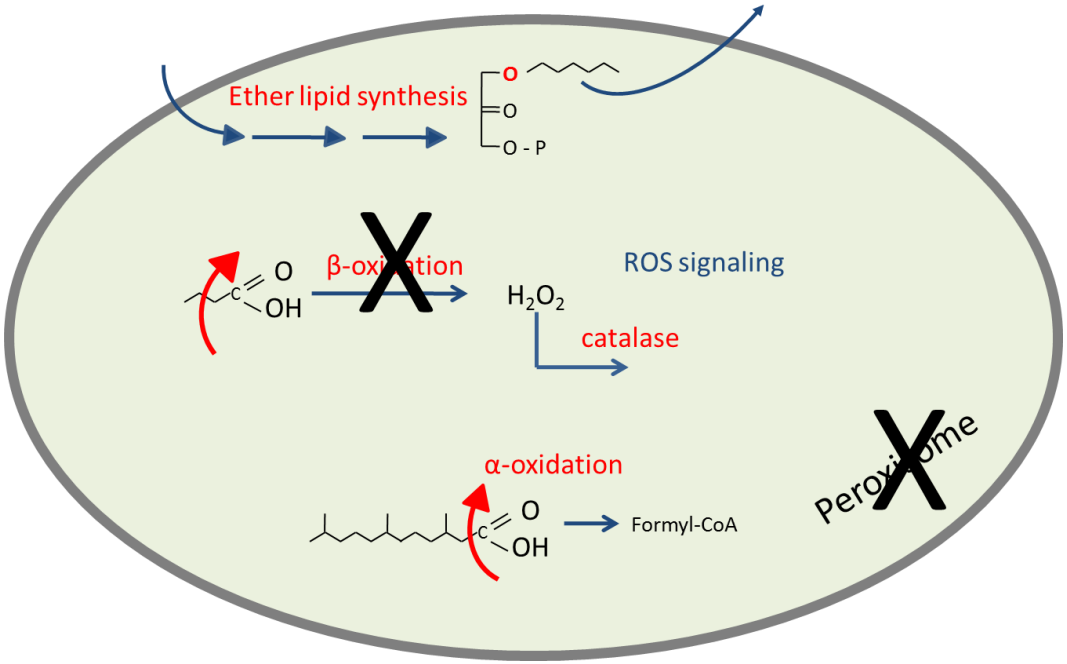
Guzenko & Strelkov (2016) Bioinformatics, pii: btw628.



Cell Metabolism

Peroxisomes: targets in rare and common diseases?

- Role in tissue functioning
- Pathogenesis using loss of function approaches in mice



Prof. Dr. M. Baes
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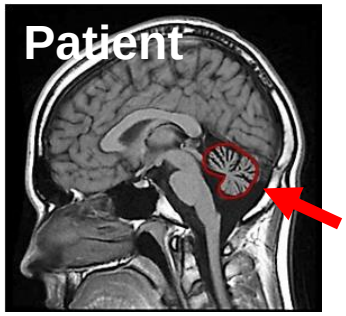
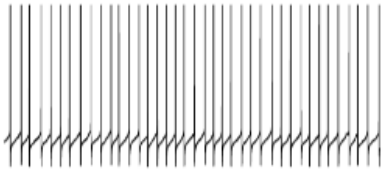
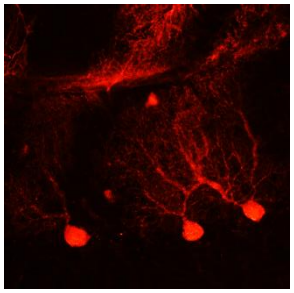
Cell Metabolism (Highlights and outlook)

- *Neurobiol of Disease,2016 :* Purkinje cell dysfunction and degeneration causing ataxia

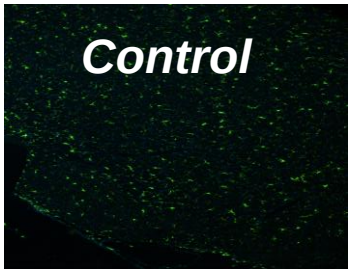


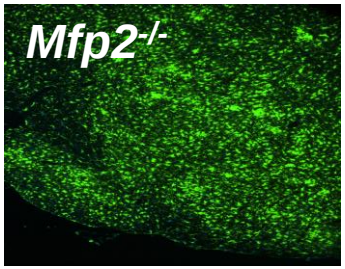
Mice





- *Glia, 2015 : MFP2 deficiency causes neuro-inflammation*





Microglia reactivity

Neuronal dysfunction

Motor
&
Cognition deficits

- Peroxisomes are essential in **β-cells** of pancreas : mechanisms?
- Peroxisomal β-oxidation is necessary for **retinal** integrity: mechanisms?
- **Microglia** : can manipulation of metabolism determine detrimental vs neuroprotective features?

Molecular Virology & Gene Therapy (Scientific Highlights)

Molecular Virology and drug discovery

- **A novel strategy for a functional cure of HIV infection**

(Vranckx et al., EBiomedicine. 2016 Jun;8:248-64.)

- **A technology platform for single virus imaging**

(Dirix et al., Scientific Reports, 2016)

- **MLL-LEDGF interaction as drug target for treatment of leukemia**

(Cermakova et al., Trends Pharmacol Sci. 2016 Aug;37(8):660-71)

Gene Therapy

- **A gene therapeutic strategy for cystic fibrosis**

(Vidovic, Carlon et al. Am J Respir Crit Care Med. 2016 Feb 1;193(3):288-98)

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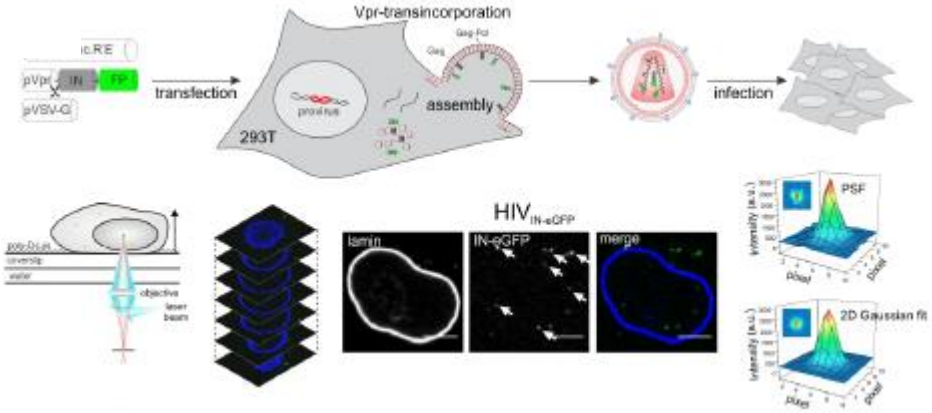
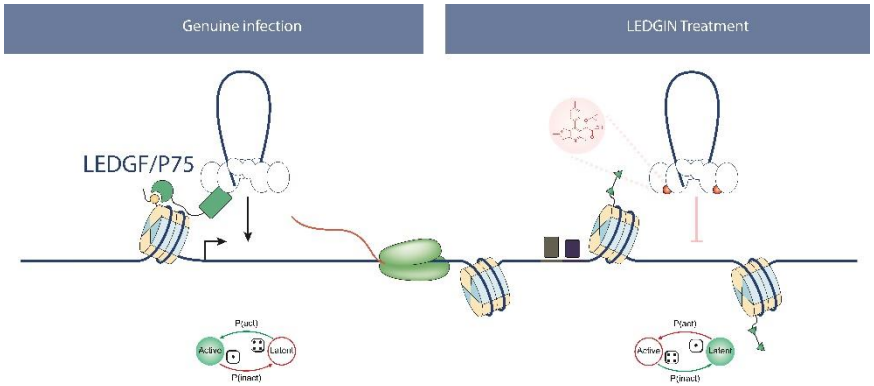
Prof. Dr. R. Gijsbers rik.gijsbers@kuleuven.be

Molecular Virology & Gene Therapy (Research lines)

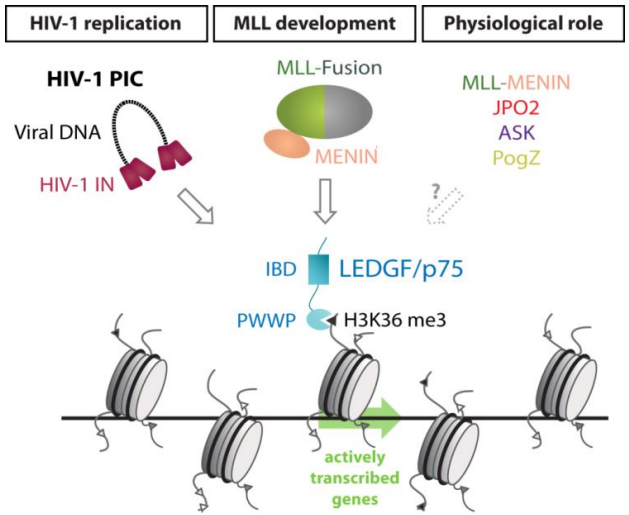
Single virus imaging of HIV



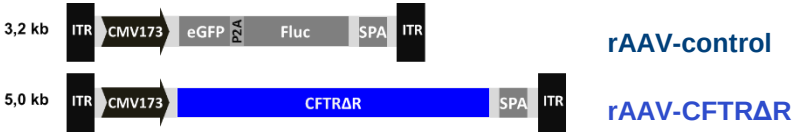
Towards a functional cure of HIV

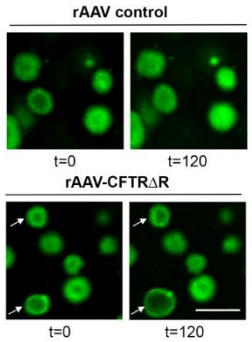


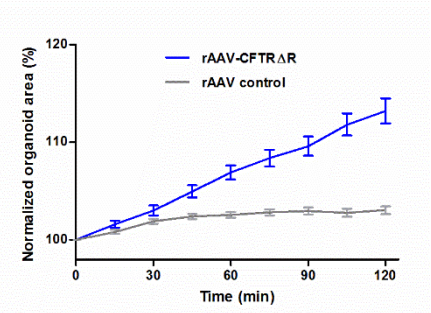
HIV points the way towards precision treatment of mixed lineage leukemia



rAAV-CFTRΔR gene transfer rescues CF phenotype in CF organoids







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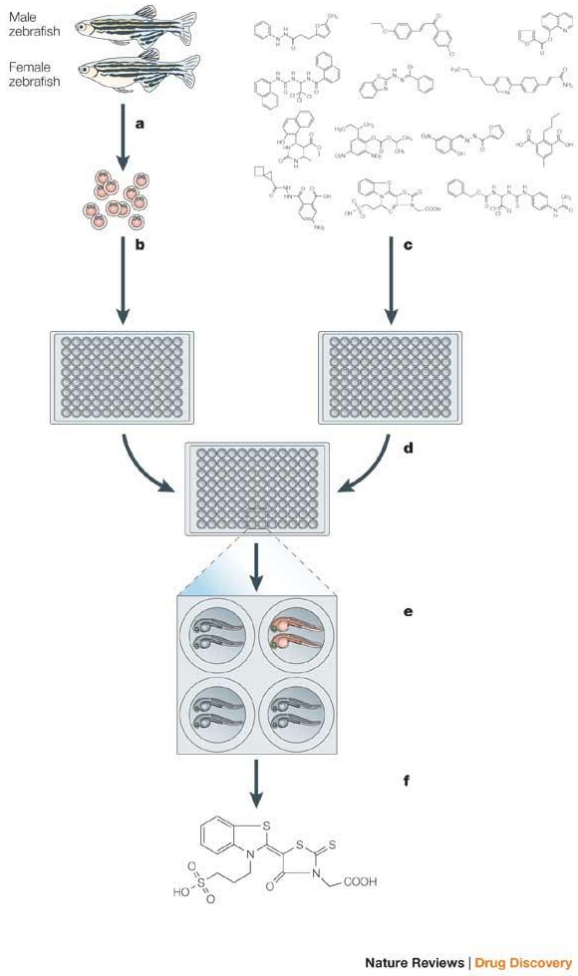
Molecular Biodiscovery



- **zebrafish transgenic lines for toxicity testing (hepato, cardio, nephro, neuro)**
- **Medaka reporter line (endocrine disruption)**
- **zebrafish transgenic and mutant lines as models for human disease (epilepsy, kidney fibrosis, cancer immunology, viral disease)**
- **66 tanks, 1200 liter**

Molecular Biodiscovery

Prof. Dr. P. de Witte peter.dewitte@kuleuven.be

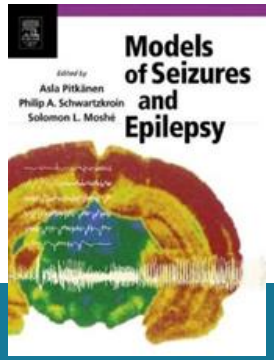
Toxicity Testing

- **Are zebrafish larvae suitable for assessing the hepatotoxicity potential of drug candidates?** *(Mesens et al, J Appl Toxicol. 2015 Sep;35(9):1017-29)*
- **Use of zebrafish larvae as a multi-endpoint platform to characterize the toxicity profile of silica nanoparticles** *(Pham et al, Scientific Reports, minor revision)*

Epilepsy models

- **Mutations in STX1B, encoding a presynaptic protein, cause fever-associated epilepsy syndromes** *(Schubert et al, Nat Genet 2014 Dec;46(12):1327-32)*
- **Gain-of-function FHF1 mutation causes early-onset epileptic encephalopathy with cerebellar atrophy** *(Siekierska et al, Neurology 2016 Jun 7;86(23):2162-70)*
- **Zebrafish models of epilepsy and epileptic seizures**

(*Copmans, Siekierska, de Witte, in print, 2nd ed, Elsevier)*



Toxicology and Pharmacology

General Research Topics:

- Drug Discovery starting from biodiversity, marine and terrestrial organisms, including purification, structure determination, and functional assays (electrophysiology, voltage clamp)
- Structure-function research of ligands (peptides, toxins, small molecules, drugs) interacting with ion channels and receptors
- Transcriptomics of venomous animals (PCR-based)
- Peptidomimetics (cyclic peptides, miniaturized scaffolds)

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Prof. Dr. Eva Cuypers
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Toxicology and Pharmacology

Scientific Highlights

- Structure-function research of ion channels and receptors
  (Nijs, M. et al., PNAS. 2016, in press)
- Toxin bio-portides: novel generation of cell penetrating medicines
  (Kerkis, I. et al., CMLS. 2016, e-pub ahead of print)
- Discovery of novel insecticides
  (Zhu, S. et al., Mol Biol Evol. 2016, 33(8):1907-20)

Objectives:

- Structure-function research of ligands - ion channels and receptors
- Peptidomimetics: cyclic peptides and miniaturized scaffolds grafted with pharmacological epitopes for novel medicines

Cloud 2 – Development of therapeutics & diagnostics

Therapeutic & Diagnostic Antibodies

P Declerck
A Gils
5 ATP, ±7 PhD, ±4 PostDoc

Radiopharmacy

G Bormans
7 ATP, 5 PhD, 5 postdocs

Medicinal Chemistry

P Herdewyn
A Van Aerschot
M Froeyen
J Rozenski
E Lescrinier
3 ATP, ±20 PhD, ±15 PostDoc

Therapeutic & Diagnostic Antibodies

Mission: generation of monoclonal antibodies (Mabs), antibody derivatives, nanobodies and diabodies and application as either therapeutics or diagnostics

Research topics:

1. Increasing fibrinolysis

- increased concentrations of **PAI-1** and **TAFI** = decreased fibrinolysis
- development and application of **immunoassays** to measure PAI-1 and TAFI
- generation, production & characterization of an anti-PAI-1/anti-TAFI diabody as a **therapeutic** to increase fibrinolysis

Prof. Dr. Paul Declerck – Dean – paul.declerck@kuleuven.be

2. drug monitoring and immunogenicity of therapeutic antibodies

- development and application of **immunoassays** to **monitor drug concentration** of therapeutic antibodies in the serum of patients
- characterization of **biosimilars**.

Prof. Dr. Ann Gils – ann.gils@kuleuven.be

3. antibody gene transfer

- development of a DNA-based platform for the ***in vivo*** **expression of therapeutic antibodies**.

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Therapeutic & Diagnostic Antibodies

Pharmabs: spinn-off

Innovation, incubation and valorisation platform on antibody development founded 2009

Therapeutic antibody development

& Antibody-based diagnostics

EU H2020 Projects and Industrial projects

Outlook:

- Develop a selected diabody as a therapeutic profibrinolyticum
- Sustain the collaboration with diagnostic companies to produce CE-labelled diagnostics & implement TDM in clinical practice
- Grow the Antibody Gene Transfer Program, and launch dedicated spinoff

Radiopharmacy

Mission: development, preclinical validation and translation to clinical use of diagnostic and therapeutic radiopharmaceuticals

Research topics:

1. small molecule based PET radiotracers

neuroinflammation	**endocannabinoid system**
TSPO, P2X7, GPR-84, CB2, ...	CB2, MAGL, FAAH,…
misfolded proteins	
amyloid, tau, …	
epigenetic targets	**ion channels (M Schönberger)**

2. biomolecule based radiotracers

This research focuses on the development, validation and translation to the clinic of **PET tracers based on biomolecules** (peptides, nanobodies, affibodies, antibodies).

- New methodology that allows room temperature radiolabeling using Al18F chelation.
- Application of PeptIns (peptides directed to aggregation-prone regions on proteins) as a new generic platform for visualisation of protein expression .

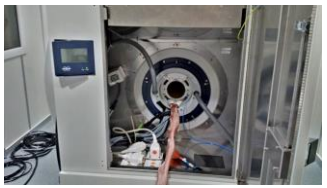
Radiopharmacy

MIRaCLe

State of the art platform for translational PET research

GMP accredited production lab

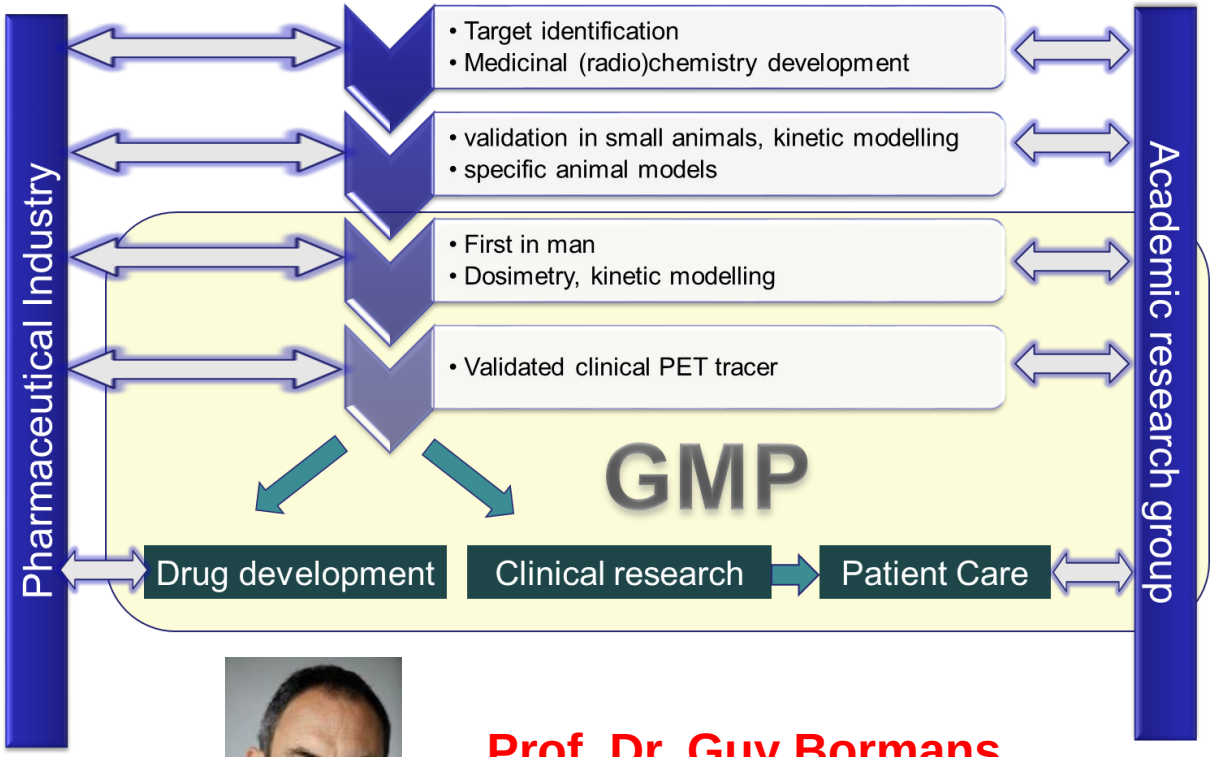
preclinical



clinical

PET/MR scanners

>15 first in man studies of novel PET tracers



Prof. Dr. Guy Bormans
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Medicinal Chemistry

Mission: transdisciplinary research focusing on lead finding, lead optimization and structure-activity relationships studies on compounds to be used as therapeutics or diagnostics; synthetic biology and directed evolution

Medicinal Chemistry Team - January 2019 status

- 6 Group Leaders
- 14 Postdoctoral researchers
- 20 PhD students
- 3 Support staff

- Combined **38 papers cited more than 100 times**
- **Over EUR 7M in research funding** generated in the last 10 years
- Successful supervision of **26 PhD students**, including many international students in the last 10 years

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Research Themes

- Drug design

Molecular Modelling
Computational Chemistry

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NMR

- Biomolecular NMR (proteins & nucleic acids)
- Structure-based design
- Small molecule characterization

Applied Organic Chemistry

- Small molecules
- Nucleosides
- Oligonucleotide Therapeutics (aptamers)
- XNAs
- tRNA synthetases

Mass Spectrometry
Analytical Chemistry

- Drug metabolism
- RNA modifications
- Electrochemistry

Synthetic Biology

- Directed evolution
- Molecular Biology

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Emeriti: 2019 + 2022

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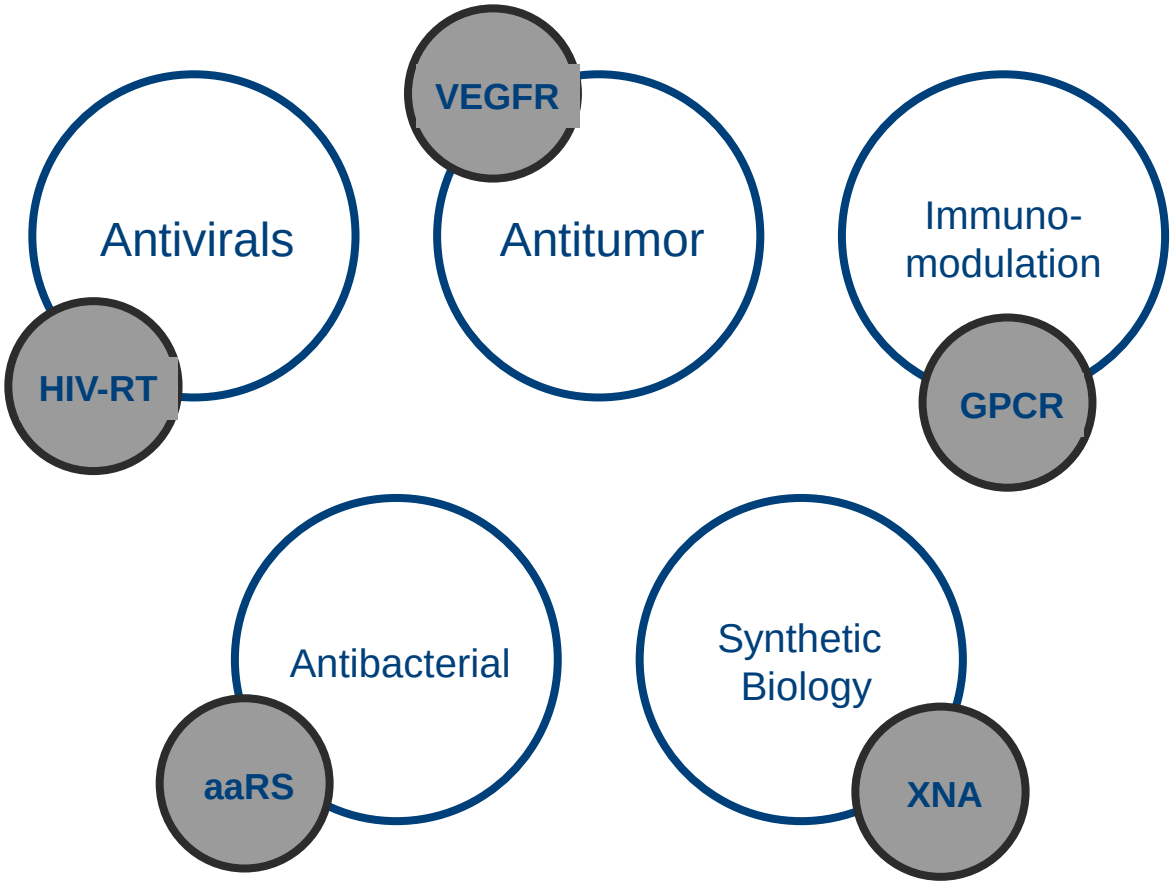
Medicinal Chemistry

Applications

Chemistry-driven

Biology-driven

Method-driven



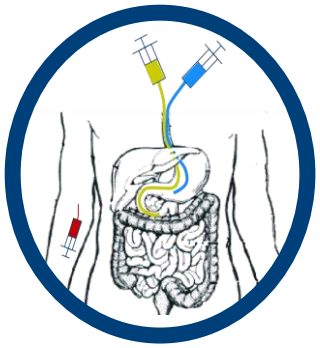
Cloud 3 – Drug delivery, disposition and (bio)analysis

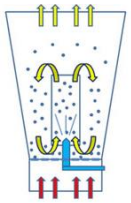
Drug Delivery and Disposition
G Van den mooter
P Augustijns
P Annaert
T Bouillion

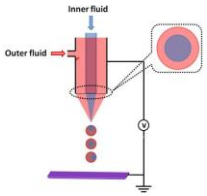
Pharmaceutical Analysis
A Van Schepdael
E Adams
D Cabooter

Toxicology & Pharmacology
E Cuypers
J Tytgat

Drug Delivery and Disposition







Patrick Augustijns

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Guy Van den Mooter

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- ✓ **General Research Topics:**
  - ✓ Intestinal drug disposition: Exploring intestinal drug and formulation behavior using a unique intestinal sampling technique
  - ✓ Pharmaceutical technology – physical pharmacy: API characteristics and formulation parameters; amorphous solid dispersions; coated nanocrystals; mAb; mesoporous silica

Drug Delivery and Disposition

Pieter Annaert

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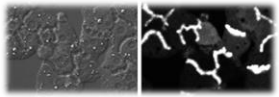
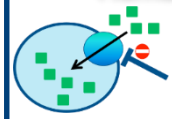
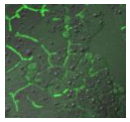


Human hepatocytes

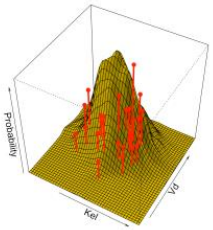


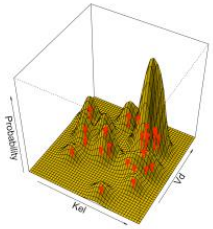
Transporter -transfected cells

Isolated perfused liver



Focus on transporter function





Thomas Bouillon

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- ✓ **General Research Topics:**
  - ✓ Hepatic drug disposition – hepatotoxicity: focus on transporter function; PBPK modeling; prediction and simulation of drug exposure
  - ✓ Pharmacometrics: PKPD relationships; transition from parametric to nonparametric methods --> optimal dose as ultimate target of modeling efforts

Pharmaceutical analysis

Ann Van Schepdael

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Advances in Capillary Electrophoresis

- **On-line screening of enzyme inhibitors**
  - Electrophoretically mediated microanalysis (EMMA)
  - Capillary electrophoresis coupled to ESI mass spectrometry
  - Development of immobilized enzyme reactors based on magnetic nanoparticles

Erwin Adams

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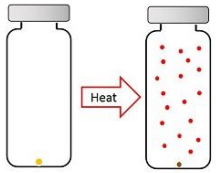
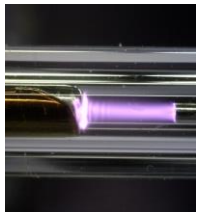
Improved sampling and detection in GC analysis

- Full evaporation technique and thermal desorption
- New detection concept based on a microplasma
- Analysis of aqueous samples, high boiling RS, halogenated VOCs,…as impurities in drugs





Pharmaceutical analysis

Deirdre Cabooter

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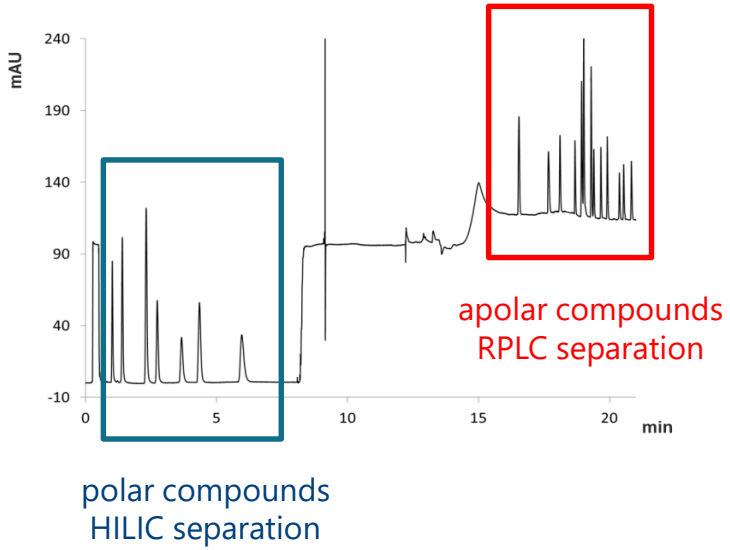
- **Novel hardware solutions for the analysis of complex samples**
  - Coupling highly orthogonal columns in series to separate polar & apolar compounds
  - Development of innovative mixing unit for online solvent exchange
  - Applications in environmental, pharmaceutical, bio-analysis…



Toxicology and Pharmacology

- **PI's:**

Jan Tytgat
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Eva Cuypers
eva.cuypers@kuleuven.be

- **General Research Topics:**
  - Discovery of buried cadavers using detection and analysis of volatile decomposition compounds
  - The use of color tests for new generation psychoactive substances
  - Alternative matrices and task-specific ionic liquids in Postmortem Forensic Toxicology
  - Imaging mass spectrometry on hair
  - Medical and forensic mass spectrometry imaging

Advances in human decomposition

✓ TD-GC/MS: Method development and validation

Anal Bioanal Chem (2014) 406:3611–3619
DOI 10.1007/s00216-014-7741-8

RESEARCH PAPER

Development and validation of a new TD-GC/MS method and its applicability in the search for human and animal decomposition products

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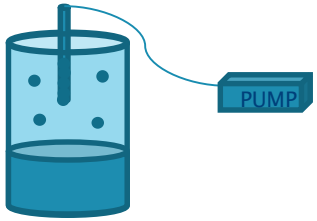

✓ Human versus animal decomposition

PLOS ONE

RESEARCH ARTICLE

The Search for a Volatile Human Specific Marker in the Decomposition Process

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Time-dependent VOC-profile of decomposed human and animal remains in laboratory environment

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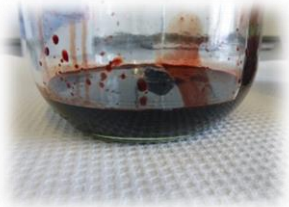
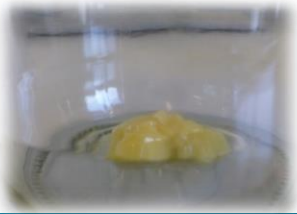
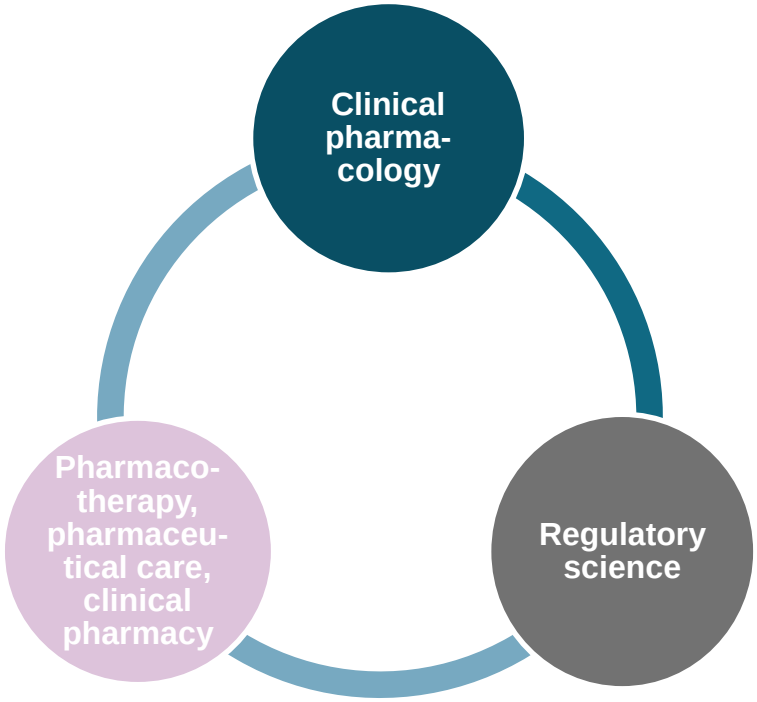
✓ Blood versus tissue





Clinical Pharmacology & Pharmacotherapy

Bridging the gap from molecule to man



Clinical Pharmacology & Pharmacotherapy

M Casteels
J de Hoon
K De Nys
V Foulon
I Huys
S Simoens
I Spriet
C Vandermeulen

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Clinical Pharmacology

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- clinical trial activities and clinical drug development,
- involving mainly healthy subjects or well-defined patient populations,
- with an emphasis on research activities in the exploratory phase (phase 0, phase Ia, phase Ib studies)
- special interests:
  - target-engagement biomarker development
  - CNS compounds / PET studies / microdosing
  - pain / analgesics
- GMP certified facilities since 2013
- Important societal roles:
  Membership of EMA Scientific Advice Working Party (SAWP) and Committee on Herbal Medicinal Products
- Chair of Belgian Drug Reimbursement Committee

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Regulatory Science

- regulatory and legal aspects of the development and market access of medicinal products, diagnostics and treatment strategies
- health economic aspects of medicinal products
- Expertise center on regulatory science topics, advising (inter)national authorities and other institutions
- Several chairs funded by industry (generics, biologics, biosimilars); various EU and IMI participations

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Pharmacotherapy, Pharmaceutical Care, Clinical Pharmacy

- **Pharmacotherapy:** with focus on the rational, efficient and safe use of medicinal products in daily patient care (both ambulatory and hospital setting).
- **Pharmaceutical Care / Clinical Pharmacy:** exploring the role of the pharmacist in the rational use of medicinal products in the ambulatory setting as well as in the hospital.
- Leadership role in developing the role of the pharmacist in research and teaching in Belgium.
- Many opportunities for collaboration around clinical PK/PD research in University Hospitals Leuven.
- Large involvement in society / committees, taking leading roles.

Hospital

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Clinical Pharmacology & Pharmacotherapy:
From research to societal relevance – a brief overview

- Membership of EMA Scientific Advice Working Party (SAWP) and Committee on Herbal Medicinal Products (HMPC)
- Chair of Belgian Drug Reimbursement Committee
- Chair of Belgian Chamber of Pharmacists
- Chair of Ethics committee UZ KU Leuven/Research
- Past Chair of European Society for Clinical Pharmacy (ESCP)
- Past Secretary of Pharmaceutical Care Network Europe (PCNE)
- Membership of BBMRI-ERIC (European Biobank Network) ELSI (ethical-legal-social) Board
- Membership of the Superior Health Council