Fidelta Overview

Sarah Harris
National Business Development

outline

- History and overall capabilities
- In *vivo*
- In *vitro*
- ADME/DMPK
- Chemistry

Sustainable track record in R&D

1952: Research Institute established by PLIVA

Azithromycin, one of world's best selling antibiotics, discovered in these labs

2006: acquired by GlaxoSmithKline

GSK Macrolide DPU and IRU Unit

2010: acquired by Galapagos

Part of R&D

2013: established as commercial CRO

Fee for service division

Quality Management

QM

Good Data Integrity Practice implemented in Fidelta

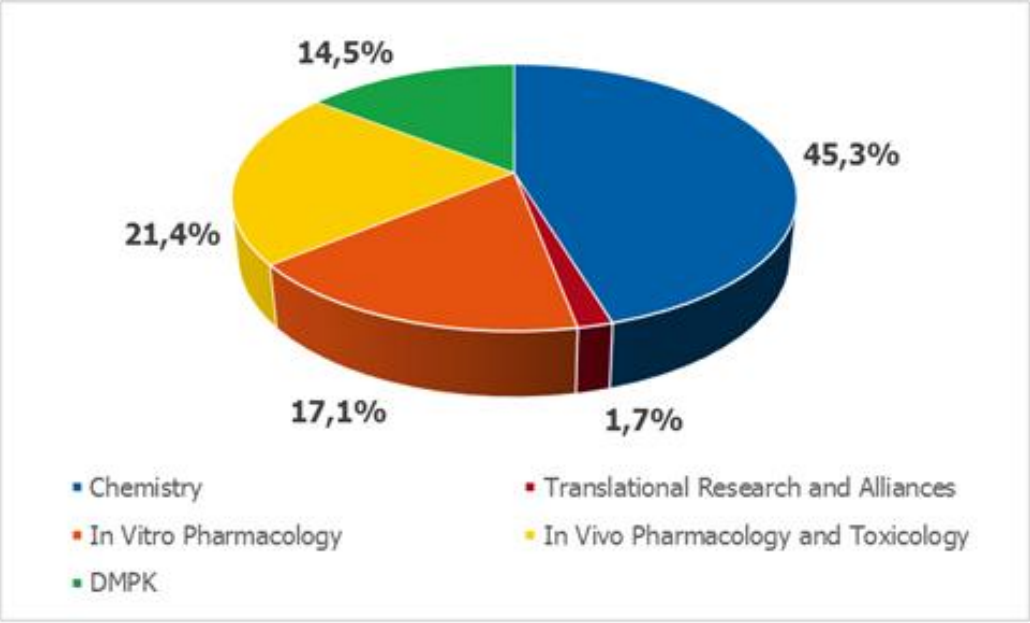
Documentation Management System

General - Procedures (SOPs); Guidelines; Forms

Scientific - Protocols, Reports, Records

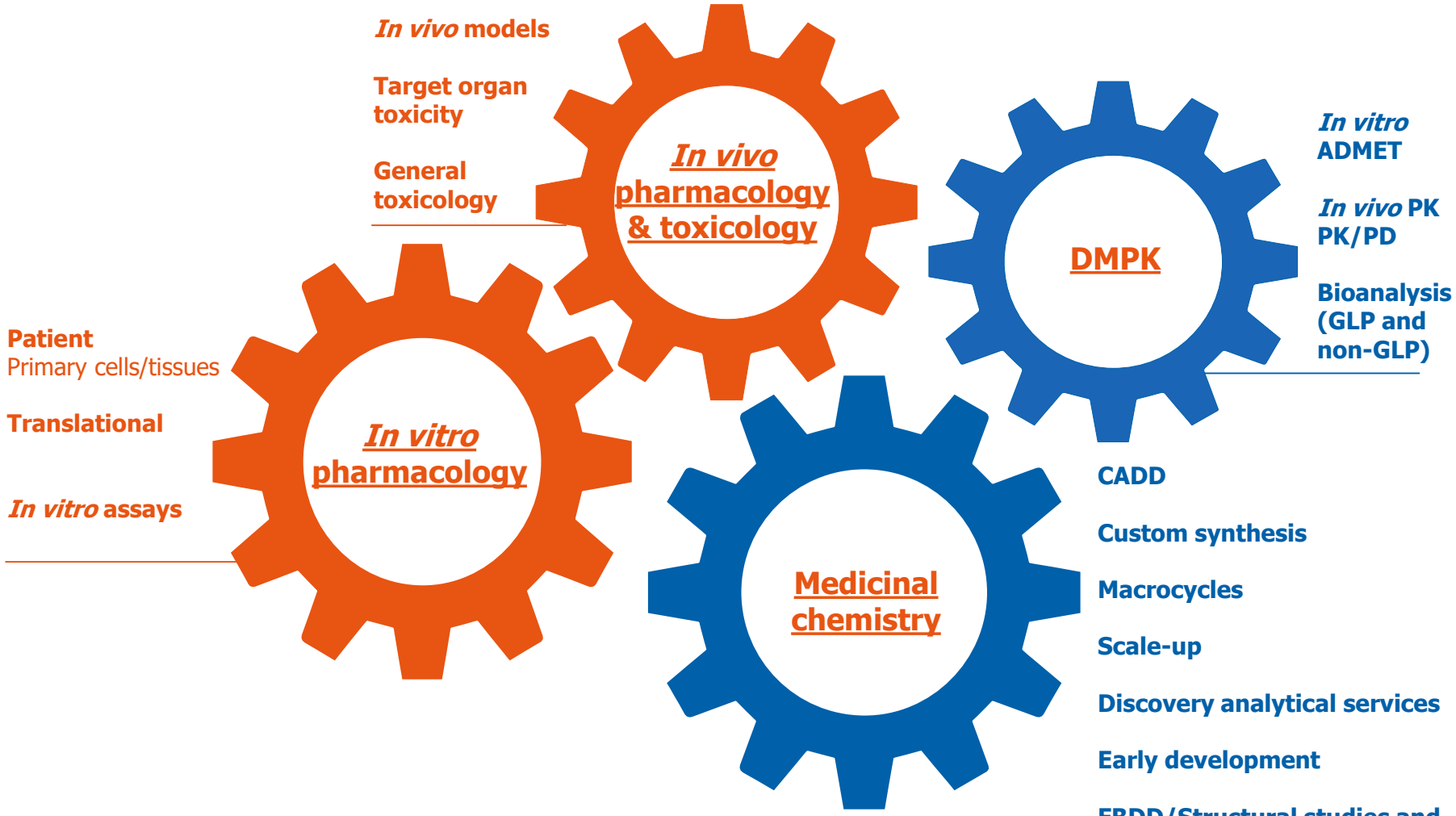
Non regulated research is conducted, documented and retained to ensure that decisions are supported by accurate and valid scientific data

Scientific team



- >120 highly qualified scientific staff, 60% PhDs, MD or DVM
- Average of >11 years of industry experience
- Big pharma and biotech heritage – combining both worlds
- >250 publications and >65 PCT applications in last decade

Integrated drug discovery at Fidelta



Fidelta Facilities and Equipment

State-of-the-Art Rodent Animal Facility

- AAALAC-I accreditation since 2009.
- 19 rooms/experimental zones
  - holding rooms and multifunctional laboratories
- BSL II barrier unit
- Ability to receive models from all vendors
- Two separate areas dedicated to non-infective and infective models
- An institutional ethical committee (CARE-Zg) is in place ensuring compliance with all national laws and regulations regarding the humane care & use of laboratory animals.

Total net surface area:
~14,000 sq ft
(1,273 m^2)

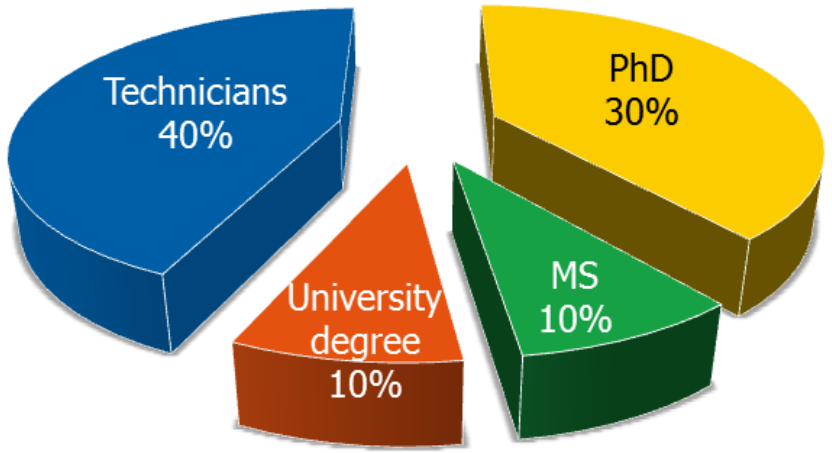
Highly skilled *in vivo* team

Average of 17 years of industry experience

- Doctors of veterinary medicine with category C in LAS
- Veterinary and laboratory technicians with category B in LAS
- Histopathologists (MD and VMD)
- Clinical pathologist with category C in LAS

- Animal welfare officer in house with category D (LAS specialist)

- *Ex vivo* and translational support:
  - molecular biologists
  - cell biologists
  - microbiologists



Established in *vivo* models

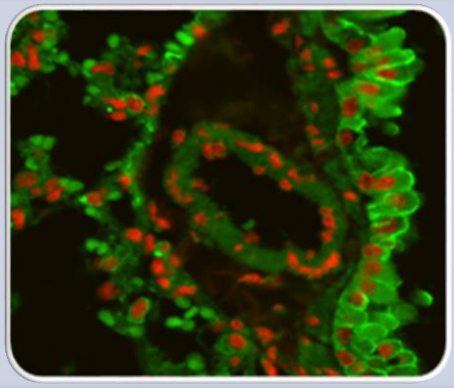
- **Routes of administration**
  - Oral (gavage and capsule)
  - Parenteral (intravenous, subcutaneous, intradermal, intramuscular, and intraperitoneal)
  - Dermal
  - Intranasal
  - Rectal
  - Ocular
  - Intracerebral
  - Intraarticular
  - Intravesical

Infection
- Bacterial
- Viral

Inflammation
- Respiratory
- IBD
- RA
- Dermatology

Oncology
- Xenograft models
- PDX

Comprehensive *in vivo* profiling



Clinical biochemistry

Full panel of automated clinical biochemistry, haematology and coagulation analyses

Histopathology

- Automated tissue processing
- Standard & special staining
- Immunohistochemistry
- Immunofluorescence
- Morphometry
- Frozen sectioning

Tailored study design

- Local and systemic routes of administration
- Clinical read-outs
- Inflammatory mediators
- Functional read-outs
- Histopathology and clinical pathology

In depth expertise in translational biomarker selection and validation

Possible Read-Outs

- Lung Function
- BAL cell counts and biomarkers
- Histopathology (IHC and ISH)
- Inflammatory mediators
- Hematology
- Clinical biochemistry
- PK/PD
- Steady state PK (LC-MS/MS bioanalysis)
- Lung explants and PCLS
- Paw Swelling
- Body Weight
- Target safety
- Colon Length
- Body weight loss
- Survival
- mRNA

Toxicology

- Non-GLP toxicity studies routinely performed in support to integrated drug discovery projects and as a service
- Team skilled in planning/outsourcing/ overseeing GLP safety assessment studies

Studies	Species
Acute toxicity study in the rat or mouse	Rat, mouse
5-day toxicity study in rodents including toxicokinetics, clinical pathology, histopathology	Rat, mouse
7-day toxicity study in rodents including toxicokinetics, clinical pathology, histopathology	Rat, mouse
14-day dose range-finding study in rodents including toxicokinetics, clinical pathology, histopathology	Rat, mouse
28-day toxicity study in rodents including recovery and toxicokinetics, clinical pathology, histopathology	Rat, mouse
MTD studies	Rat, mouse
Local tolerance studies	Rabbit

Highly experienced toxicology team comprising certified toxicologist, toxicological pathologist and clinical pathologist

In vitro pharmacology

- Development and validation of biochemical & cell-based assays
- *In vitro* compound screening to support hit/lead identification and optimization
- Translational research & strategies
  - *in vitro* assays on human tissue samples (healthy donors and patients)
  - *ex vivo* analyses for biomarker selection



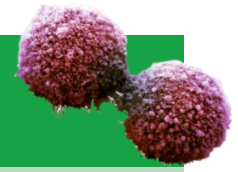
In vitro pharmacology

Therapeutic areas

Inflammation

- Disease relevant assays in human primary cells
  - Mediator release
  - Cell surface and intracellular markers expression
  - Proliferation
  - Chemotaxis
- Indications in focus:
  - Inflammation
  - Respiratory
  - RA
  - Gastrointestinal
  - Fibrosis

Oncology

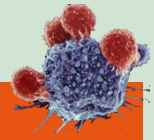


- Target validation
  - Expression in diseased tissue
  - Silencing or overexpression
- Cell proliferation
  - 2D
  - 3D

Infection

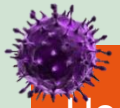
- Bacteria
  - In house strain collection
  - Access to clinically relevant pathogens
  - Antimicrobial susceptibility testing
  - Compound profiling
    - resistance development propensity
    - time-kill
    - biofilm studies
- Viruses
  - Rhinovirus and influenza virus
  - Antiviral activity

Immuno - Oncology



- Immune checkpoints
- Tumour infiltrating cells

Host-pathogen interactions



- Modulation of host response to viral infection

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Foundations of translational offerings

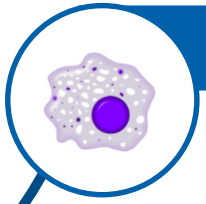
- Expertise and track record in integrated drug discovery and development up to Phase II
  - Inflammation (respiratory, GI, RA) and infection

Clinics

- Experience with clinical studies, human sample collection and analysis
- Close collaboration with clinical community
- Access to samples from healthy volunteers and patients

In vivo

- State of the art AAALAC accredited animal facility
- More than 50 animal models in place

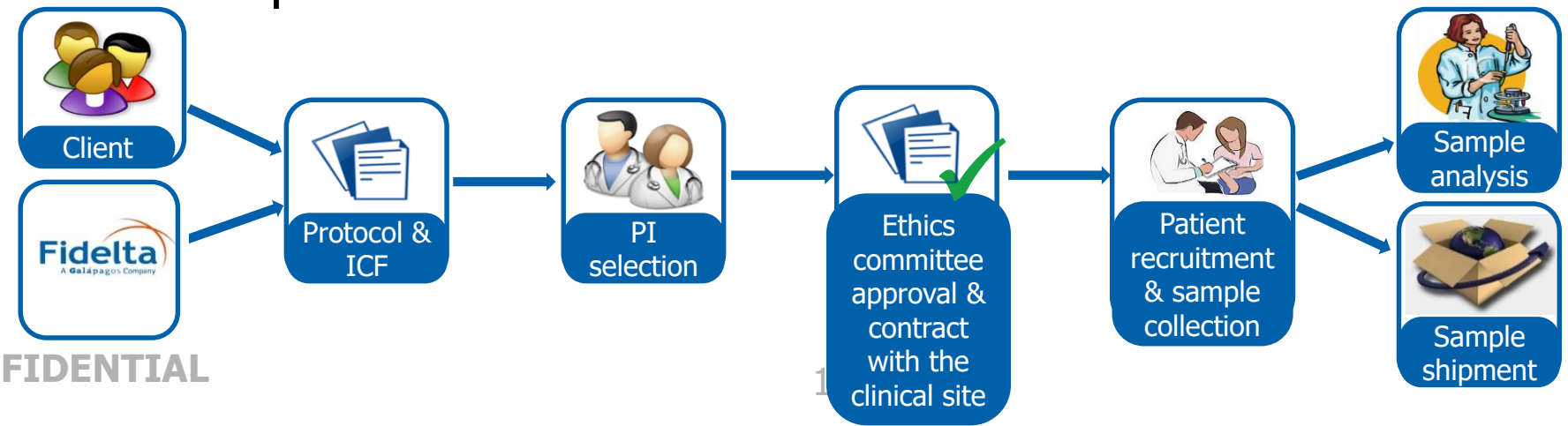


In vitro

- Testing systems in primary human cells, patient samples and tissues

Ethical and regulatory compliance

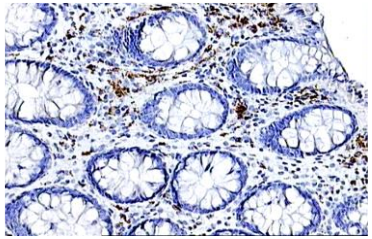
- High quality ethically obtained human tissues from consented patients
- Procedures harmonized with international legislature
  - The Human Tissue Act 2004, EU laws and regulations, etc.
- Human biological sample management implemented in 2007
  - In line with GSK Policy
- SOP-s covering human sample collection and management
- GCP compliance



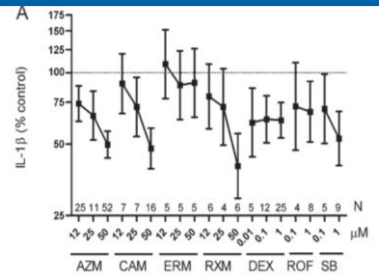
Patient sample studies

- Prospective medical research studies on carefully selected patient population
  - Detailed medical information
  - Sample types: tissue, blood and biological fluids
  - *Ex vivo* studies and sample analysis within 30-60 min from sampling
- Research on FFPE tissue samples
  - Tissue repositories of collaborating hospitals
- Scope
  - Biomarker research
  - Target validation
  - Compound testing
  - Assay development for early readouts of efficacy in Phase I

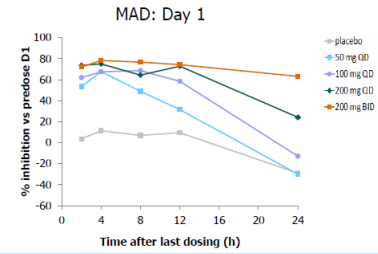
Target expression



Compound testing



Phase I efficacy readout



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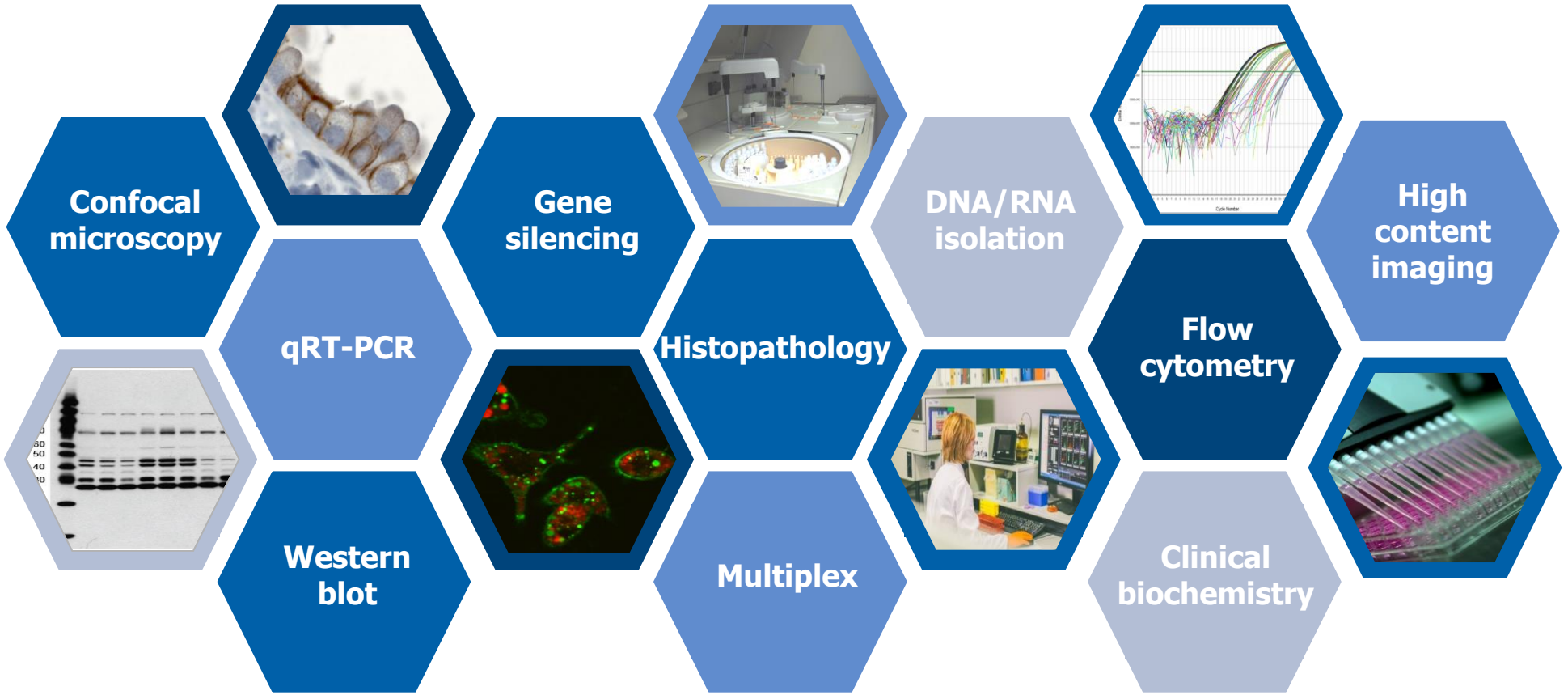
Sample analysis



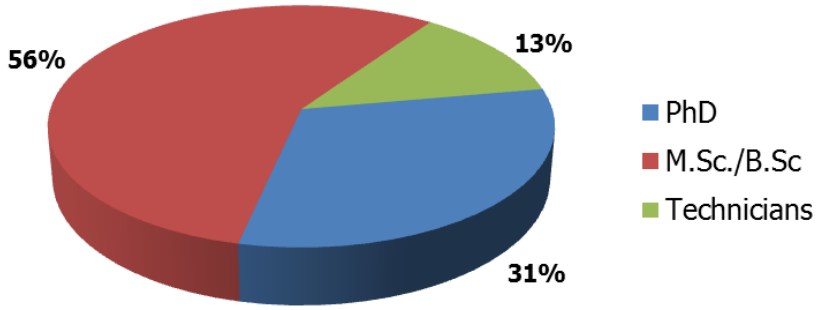
DMPK Services

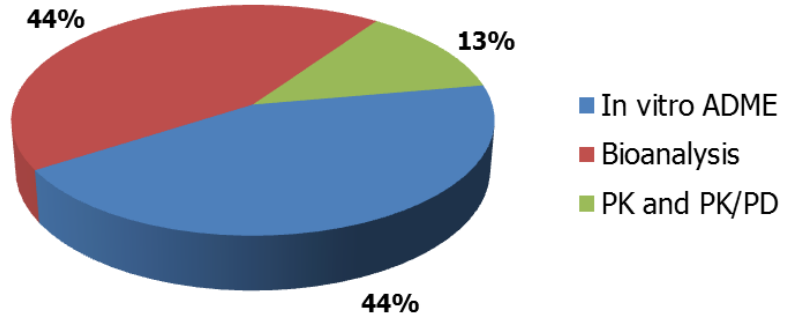
- Broad range of *in vitro* ADME assays
  - Standard and customized layouts
- Preclinical Pharmacokinetics
- PK/PD and Toxicokinetic analysis
- Bioanalysis:
  - non-GLP and GLP-compliant bioanalysis
  - Biomarker analysis

Available within integrated projects and as stand-alone services

Our team

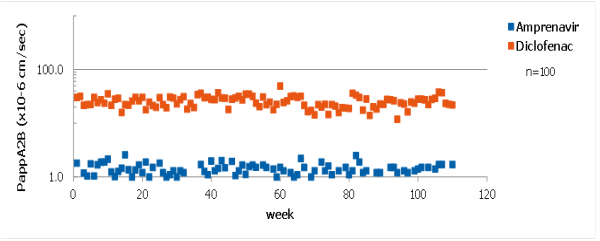
- Team of highly experienced scientists focused on providing high quality, rapid ADME/PK data and support to projects
  - proven track record
  - experienced in working with international teams
  - average of 10.8 years of industry experience





Focused to deliver

- High quality and reproducible data
  - assay controls continuously tracked and included in each assay
  - semi-automated and automated assay layouts
  - numerous assays cross-validated with clients
- Rapid turnaround time
  - 5-10 day turnaround depending on assay set-up
  - maintenance contracts in place for critical equipment
- Meeting customer and project needs
  - flexible assay formats, protocols and reporting templates
  - experienced staff to provide guidance
  - assay packages tailored to meet project requirement



In vitro ADME platform

Permeability	Binding	DDI
➢ Cellular permeability • MDCK, MDCK-MDR1 • Caco-2 ➢ Artificial membranes • PAMPA	➢ Plasma protein binding ➢ Blood Partitioning ➢ Tissue Binding ➢ Microsomal binding	➢ Inhibition • CYP450 direct inhibition & MDI (recombinant, HLM) ➢ Reactive metabolites • Glutathione trapping
PhysChem	**Metabolic Stability**	**Metabolite Profiling & ID**
➢ Kinetic solubility ➢ Thermodynamic solubility • pH, SGF, FeSSIF • ChromLogD	➢ Microsomes, S9, Hepatocytes ➢ Recombinant enzymes ➢ Plasma and blood ➢ SGF, FeSSIF	➢ Reaction Phenotyping ➢ Aldehyde Oxidase ➢ Metabolite Identification • Interspecies Profiling

A battery of standard assays available to rapidly progress compounds through discovery stages

Examples of *in vitro* assays run as weekly screens

- Permeability & Pgp substrate assessment in MDCKII-MDR1
- Distribution
  - PPB (ED), microsomal binding
- Metabolism
  - Drug-drug interactions
    - CYP450 direct inhibition (recombinant, HLM)
    - CYP450 MDI (HLM, recombinant 3A4)
  - Metabolic stability:
    - Microsomes, Hepatocytes
  - Plasma and blood stability

In vivo Pharmacokinetics

- In-life phase undertaken our AAALAC accredited, state-of-the art, animal facility
  - Available Species: Mouse, Rat, Rabbit
  - In life-phase for other species is subcontracted
  - Certified veterinary staff
  - Animal Welfare Officer
  - Institutional Ethics Committee in place
- Standard and custom PK designs employing various routes of administration and sampling

Flexible PK study designs

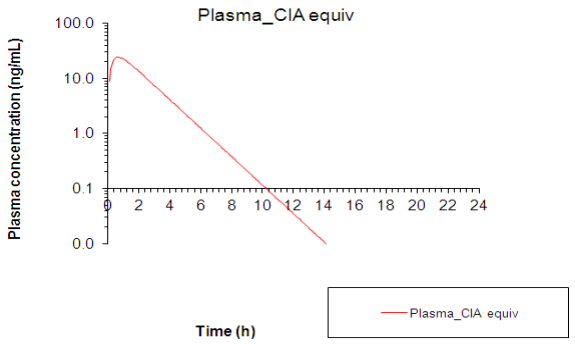
Routes of Administration	Sampling Methods	Sample types
• Intravenous, Oral • Subcutanous, intaperitoneal, intramuscular, intradermal, topical • Intranasal, intratracheal • Intracolonic	• Serial sampling ○ Tail- vein, saphenous vein • Catheter (jugular, femoral) • Heart puncture (terminal)	• Whole blood, plasma, serum • Tissues/organs • Excreta (urine, feces) • Cerebrospinal fluid (rat)

Types of studies

- Rapid screening studies to assess exposure
- PK studies to estimate
  - disposition kinetics and bioavailability
  - dose proportionality
  - routes of excretion (metabolic cages)
- Customized studies (intestinal loops)
- Single and repeated dosing

Non-Clinical Pharmacokinetics

- Non-compartmental and comparmental modeling (WinNonlin)
- Allometric scaling and human dose predictions
- Toxicokinetics
- PK/PD



Eur J Drug Metab Pharmacokinet
DOI 10.1007/s13318-011-0074-5

ORIGINAL PAPER

Investigating the barriers to bioavailability of macrolide antibiotics in the rat

Jasna Padovan · Jovica Ralić · Vatroslav Letfus · Astrid Milić · Vlatka Bencetić Mihaljević

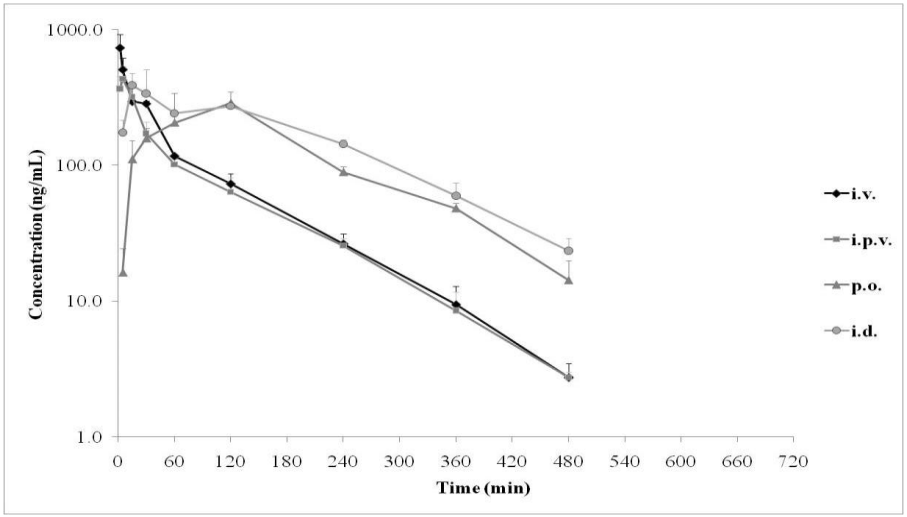


Fig. 3. Blood concentration-time profiles following intravenous (i.v.) and portal-vein (i.p.v.) administration at 2 mg/kg and oral (p.o.) and intraduodenal (i.d.) administration at 10 mg/kg for CLA

Bioanalytical capabilites

- GLP Bioanalysis
  - Method Development and Validation
  - Sample analysis from rodent and non-rodent GLP toxicology studies
  - Sample analysis from Clinical studies
  - Successful GLP inspection in 2015
- Non-GLP Bioanalysis
  - High throughput bioanalysis to support *in vitro* ADME screening
  - Method development for preclinical pharmacokinetic (PK), toxicokinetic (TK) studies and pharamcodynamic studies

Qualified methods providing high quality and fast turnaround

Bioanalytical capabilites

- Biomarkers
  - Customized assay development
  - *In vitro/in vivo* and clinical samples
- Metabolite Identification and Profiling
  - LightSight Software
  - *In vitro* and *in vivo* Metabolite Analysis
- Reactive metabolite trapping (GSH)

Extensive mass spectrometry capability and experience

Instrumentation

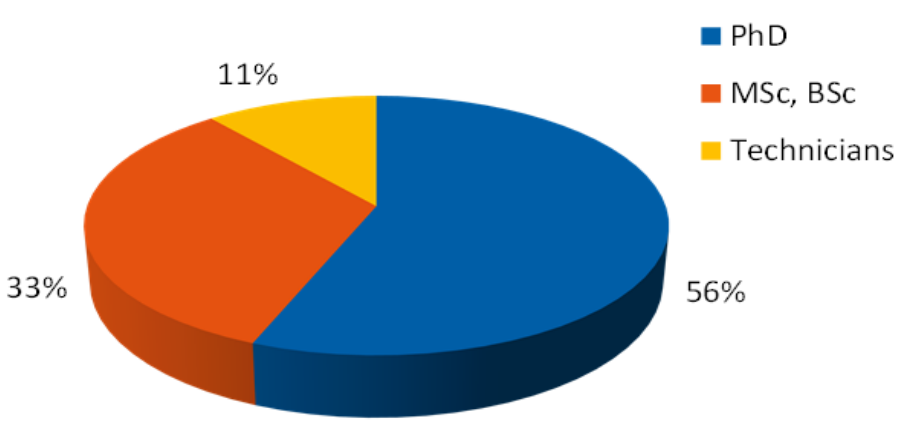
- Analytical equipment
  - 2x Shimadzu Nexera UHPLC /**API5500** MS
  - 1x Shimadzu Nexera UHPLC/**API6500** MS
  - 3 x Shimadzu Nexera UHPLC /**API4000** MS
  - 2 x Shimadzu Nexera UHPLC /**API4500** MS
  - 1x Agilent HP 1100 binary LC/CTC HTS/X PAL/**API4000** MS
  - 1x 1290 Infinity& Agilent 6540 Q-TOF
- Software
  - DiscoveryQuantTM 3.0
  - LightSight Software
- Automated liquid handling systems
  - 2xTecan Evo and Perkin Elmer Janus

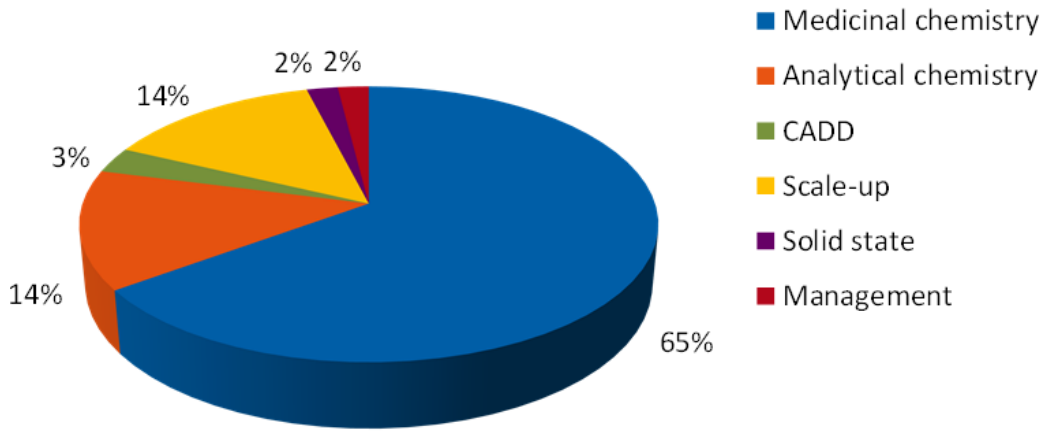
Maintenance contracts in place for all analytical equipment

Chemistry

Chemistry team

- Team of highly experienced and capable scientists who design and make compounds
  - proven track record
  - experienced in working with international teams
  - average of 12.7 years of industry experience





Synthetic and Medicinal Chemistry

- Strong synthetic and medicinal chemistry expertise

- Experience across a
  - whole range of chemistries and structural classes
  - small heterocyclic compounds to macrocycles

Scale Up Chemistry

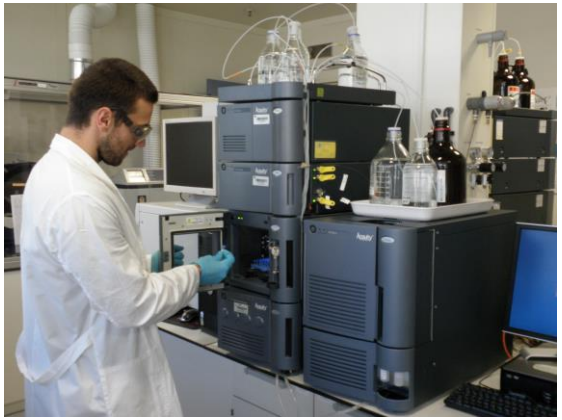
- Route optimization, synthesis of metabolites, impurities and degradation products, standards, custom intermediates
- Scale up to 1 kg
- Equipment:
  - 4 double-jacketed glass reactors (2, 5, 10 and 20L)
  - 4L hydrogenation autoclave
  - temperature range: -70°C to +150°C
  - 10 & 20L rotary evaporators
  - in-process analytical chemistry involved
  - rapid transfer from small to large scale

Structural studies and interactions

- Structural studies
  - identification and structure characterization
    - by-products
    - impurities
    - degradation products
    - unexpected result of chemical reaction
- Relative stereochemistry
- Solution-state conformations
- Ligand-receptor interactions
- NMR screening for FBDD

Analytical services

- Achiral and chiral purity assessment (LC)
- UPLC/HPLC method development and transfer
- MS- and UV-directed purifications
- HPLC separation of:
  - NCE and API
  - drug substances
  - impurities and process related substances
  - degradation products
- Generic LC-DAD-MS platform for QC analysis
- HT lipophilicity (ChromlogD/CHI) and HT permeability (IAM)



Early development services

- Solubility
  - organic solvents, bio-relevant media (SGF, FaSSIF, FeSSIF), buffers, aqueous media with solubility enhancers
- Stability
  - solution and solid state stability
  - light stability (ICH conditions)
- Accelerated aging
- Forced degradation
- HT lipophilicity/HT solubility
- CHI

- Solid state characterization
  - XRPD, TGA, DSC, FT-IR
  - hot stage and optical microscopy
  - single crystal X-ray diffraction
- Form and version screening
  - polymorphs, salts, co-crystals