Furthermore, we have the flexibility to
through to candidate selection.

studies from early target validation
in vivo hunting expertise, supports
extensive biopharmaceutical and drug
of highly experienced scientists with
macology team (> 70 staff), consisting
phar and infectious disease. Our
disease and complications, oncology
key therapeutic areas of CNS, metabolic
pharmacology expertise in our
in vivo Evotec has developed considerable
Executive Vice President In vivo Pharmacology
Fraser McIntosh
OFFERING
Evotec has developed considerable in vivo pharmacology solution for your drug discovery
programme; whether that’s an off-the-shelf standard protocol or
developing bespoke assays / read-
outs for your specific requirements. We utilise a plethora of acute, mechan-
istic, pharmacodynamic models relevant to the target biology to assess
target engagement and establish PK / PD relationships. Our efficacy
models are used to assess biological effects on pathophysiology’s relevant
to the disease of interest and are validated with appropriate standards
care and supported by rigorous statistical methods. At Evotec we are
continually striving to develop in vivo models and endpoints with greater
translational relevance to the clinic and all our models can be supported by
relevant pharmacokinetic measurements to determine exposure
effect relationship. Importantly, Evotec’s in vivo pharmacology func-
tions are typically co-localised with our in vitro pharmacology units
and this complementarity leads to
disease biology platforms with a
stronger disease focus and breadth
of expertise.

CENTRAL NERVOUS SYSTEM (CNS)
ACUTE/CHRONIC PAIN
Evotec offers a range of acute and chronic pain models in rodents with
different read-outs depending on the
model of interest. Importantly, our
scientists are fully blinded to reduce
the potential for operator bias.

Pain Models
Spinal Nerve Ligation model (SNL); Visceral pain: colorectal / vaginal
distension-induced visceromotor reflex; CFA-induced Inflammatory
pain: Formalin induced nocifensive behavior, mustard-oil induced
neurogenic inflammation

Key Read-outs
Thermal sensitivity: Hargreaves Test, hot plate, tail flick
Mechanical sensitivity: Von Frey test, pressure application measure-
ment device, dynamic weight bearing
Laboras automated recording for
formalin paw and locomotor activity
Visceral motor reflex-EMG activity

IN VIVO PHARMACOLOGY

Fraser McIntosh
Executive Vice President In vivo Pharmacology

ONCOLOGY
Evotec offers a range of rodent
models, spanning xenograft, syngeneic
and orthotopic models coupled with
the possibility of a broad range of
efficacy and biomarker read-outs.
In addition, we have access to a
range of relevant human tumour
samples via the Institut Universitaire
du Cancer Toulouse Biobank which
will be utilised for biomarker studies
or ex vivo evaluations including
compound treatment.

Oncology models
Subcutaneous human xenograft
models. Syngeneic models suitable
for the evaluation of immuno-oncol-
ogy therapies Orthotopic models
including: Bladder, brain, breast,
colon, kidney, liver, lung ovary, skin.
Suitable for metastasis studies.
Angiogenesis models (in mice and
rats), with Laser Doppler

Adjacent sections (20 μm), male Sprague Dawley rat, 8 weeks old
1 nM ‘[H]-naloxone

ADENO-ASSOCIATED VIRUS (AAV)
TARGET VALIDATION PLATFORM
Neonatal and adult (stereotaxic)
 injections into specific brain regions
in rodents using AAV-vectors
designed for knock down or over-
expression of specific proteins to
support target identification.

Key Read-outs
Behavioral assays, histology and
immuno-histochemistry (IHC),
morphometric analysis
High-content IHC analysis
Biomarkers (e.g. cytokines using
Mesoscale)

EX VIVO RADIOLIGAND BINDING AUTORADIOGRAPHY
(ARG) PLATFORM
Beta Imager allows fast screening.
Phosphorimager for high resolution
images. Multiple applications:
KD and Bmax determinations in
specific tissue regions
Receptor / protein localisation

Functional responses:
GTPγS radioligand binding as
a marker of G protein-coupled
receptor (GPCR) receptor activation
Ex vivo receptor occupancy to
determine target engagement
Key Read-outs
- Efficacy evaluation by tumour volume and/or Bioluminescence (IVIS Spectrum) imaging for 3D tomography and metastasis.
- Full Hematological analysis including FACS analysis
- Bioanalysis for associated pharmacokinetic studies (PK/PD)
- Tissue sampling for:
  - Genomics studies including: RT-PCR, Taqman, TLDA
  - Protein analysis (total and phosphorylated protein profiling)
  - ELISA, Western Blotting, dot-blotting, histology, immunohistochemistry
  - Quantitative image analysis (Definiens technology)
- Mitochondrial metabolism:
  - Cellular ATP generation: Glycolytic vs mitochondrial pathways
  - Oxygen Consumption Rate (OCR) and Extracellular acidification rate (ECAR)
- Oxphorygraph: a way to analyse the isolated mitochondrial function
- Mitochondrial membrane potential, respiration rate, phosphorylation rate
- Metabolite analysis for quantification of lactate, glucose, glutamine, glutamate
- Microdialysis
  - Detection of metabolites and/or drug levels by ex vivo microdialysis in tumour, brain, adipose tissue or biological fluids

Metabolic and Diabetic Complication
Metabolic diseases like Diabetes mellitus, obesity or the metabolic syndrome belong to the major chronic diseases in the world. Long-term Diabetes mellitus results in a number of severe diabetic complications impairing kidney, eyes, heart and peripheral nerve function.

Animal models of metabolic diseases include genetic models (i.e. ZDF rats, INS2 Akita mice), diet-induced models using different diets, chemically-induced models with Streptozotocin (STZ) or Alloxan as well as a humanised beta-cell model where human islets are transplanted into STZ-treated diabetic NOD-SCID mice.

Relevant animal models of eye disease for proliferative and diabetic retinopathy have been developed and validated. These include models of chemically induced diabetes (i.e. STZ) as well as a model of Oxygen Induced Retinopathy (OIR).

All metabolic and diabetic complication animal models are run under standardised conditions and profiled with a variety of supporting read-outs:

- Standard Read-outs
  - Standard clinical and metabolic read-outs including functional glucose/insulin tolerance test; ex vivo read-outs including RT-PCR, biochemical assays, hormonal status and histology.

Advanced Read-outs
Hyperinsulinemic euglycemic clamp, food intake profiles, pairfeeding, body composition analysis by Nuclear Magnetic Resonance (NMR) spectroscopy, morphometric analysis with customised algorithms e.g. with pancreas and adipose tissue, blood pressure analysis, assessment of Glomerular Filtration Rate (GFR).

Biomarker approaches
Plasma and tissue analysis (e.g. ELISA, quantitative RT-PCR), high-content tissue imaging for bright as well as immune histostaining, single and multiplexing on the Mesoscale platform, e.g. cytokines, mass spectrometry (ie. LC-MS/MS).

Infectious Disease
Evotec specialises in assessing the efficacy of lead and candidate compounds in highly relevant and validated models of infection. Our extensive range of established models is well-suited to the development of multiple classes of agent including small molecules, natural products, peptides, antibodies, other biologics and vaccines. We provide a highly bespoke service, customising studies to meet the exact requirements based on programme needs and parameters / endpoints of interest.

Models of Infection
For efficacy assessment against bacterial and fungal infections, our models address different sites of infection (localised and systemic) and pathogens by Gram-positive (including Staphylococcus aureus, Streptococcus pneumoniae, and others), Gram-negative (including Pseudomonas aeruginosa, Escherichia coli, Acinetobacter baumanii and others), anaerobes (including Clostridium difficile) or fungal species (including Candida sp., Aspergillus sp., Mucorales, Malassezia sp.).

In particular, Evotec specialises in PK/PD profiling and modelling of antimicrobial agents in multiple disease models in order to understand the key drivers for efficacy and translation of data into clinical trial design.

Key Read-outs
- Burden at site of infection and in multiple biological matrices including quantitative culture, QPCR and biomarkers
- Microbiome analysis and sequencing
- Bioluminescence (IVIS Spectrum) imaging.
- Host response endpoints including ELISA, Western Blotting, dot-blotting, histology, immunohistochemistry, cytokine profiling and cytometry

Advanced Read-outs
- Bioanalysis for associated pharmacokinetic studies (PK/PD) and pathogen-associated biomarkers

Infectious Disease
- Analysis platform

The combination of in vivo pharmacology with histology techniques offers a powerful tool to further analyse disease relevant biomarkers. Whereas histology and IHC helps to identify disease and target relevant changes, automated morphometric analysis can yield unbiased quantitative information amenable to statistical analysis, which adds significant value to the customers drug discovery effort. Furthermore, histopathology on critical organ systems will allow early risk assessment.