



## Neuroscience Drug Discovery and Development Capabilities

Aptuit's site in Verona, Italy, offers long-standing scientific expertise and specialized knowledge of integrated drug discovery and development in the Neuroscience area. From our Verona facility, more than 400 highly-skilled drug discovery and development experts, state-of-the-art equipment and scientific tools enhance Aptuit's ability to constantly provide our clients the best science, service, and people in the industry. The site has a world class reputation for neuroscience discovery and development, spanning Psychiatry and Neurology diseases. It can support all phases of the Drug Discovery process, from Target Validation to Candidate Selection, FTIH and beyond, that are fully integrated with other preclinical disciplines.

Our fully integrated approach includes working closely with colleagues in Medicinal Chemistry and DMPK, Toxicology and Pathology and Clinical Sciences, allowing us to produce high-quality candidates and reduce candidate attrition rates. We have preclinical and clinical experience in a wide variety of target types including: GPCR targets, ion-channels, transporters and enzymes (see below).

Moreover, individual packages of pharmacological services are offered based on a specific phase of the process (e.g. Target Validation, Hit Generation, Lead Characterization etc); and/or through specific assays or tests (e.g. selectivity/liability panel, mode of action studies, receptor occupancy, *in vivo* efficacy models and liability assays (CNS, abuse potential, cardiovascular and respiratory liabilities).

Our substantial experience in Translational Biology strategies provides robust integrated data packages to bridge effectively the preclinical/clinical interface to facilitate data driven decision making that increases the probability of clinical success.

Studies are designed to suit individual compounds under evaluation and to accommodate clients' specific requirements. These may include late stage differentiation studies, problem solving, new indication studies, consulting and due diligence.

Our productivity track record over the past decade includes:

- ➔ 25 Candidates selected
- ➔ 28 Phase I initiations
- ➔ 15 Candidates initiated Phase II
- ➔ 3 Phase III initiations
- ➔ 2 Filings submitted
- ➔ 500 peer reviewed publications
- ➔ 30 patents

### Neuroscience Target Experience Includes:

**GPCRs:** Orexin: OX1, OX2; Neurokinins: NK1, NK2, NK3, Vasopressin/oxytocin: V1b, OT CRF: CRF1, CRF2; Neuropeptide Y: NPY1, NPY2, NPY5; Neuropeptide S: NPS; Neuromedin U: NMU1; Muscarinic: M1; Dopamine: D2, D3; Histamine: H1, H3; Serotonin: 5-HT1a, 5-HT1b, 5-HT1d, 5-HT2a, 5-HT2c, 5-HT6, 5-HT7; GABA: GABAB; Glutamate: mGluR1, mGluR2/3, mGluR4, mGluR5, mGluR7; CCK: CCK1, CCK2; Ghrelin; Melatonin: MT1, MT2; Orphan receptors/novel targets – experience with target validation on orphan receptor systems

**Ion channels:** NMDA: broad range of subunit configurations; Allosteric Glycine site on NMDA-R; Sodium Channels: Nav1.2, Nav1.3, Nav1.7, Nav1.8, Nav 1.5; Potassium Channels: Kv3.2, Kv1.1, Kv1.2 and Kv1.4; GABA: GABAA; Nicotinic: alpha7; AMPA

**Transporters:** Glycine: GlyT1; Monamine: DAT, NET, SERT

**Others:** Enzymes: PDEIV, NOS, MAO-A, MAO-B, Cox2, SIRT



#### Neuroscience Techniques and Experience Includes:

##### Pharmacology and Translational Biology

- Molecular and Cellular Biology
  - RNA/DNA and Cell Biology Assays
  - Biodistribution and proteomics
  - *In vitro/In vivo* gene manipulation
- Electrophysiology
  - Manual patch-clamp assays (hERG and selected ion channels) in recombinant and native cellular/brain slice systems
  - Rapid Ice (hERG and selected ion channels)
  - *In vitro* extracellular recording
  - Automated patch clamp assays
- *In vitro* Pharmacology
  - Liability/selectivity panel
  - Hit identification
  - Assay generation
  - Cell based assays
  - Primary culture pharmacology
  - Lead Optimization package
  - *In vitro* profiling for GPCRs, ion channels, transporters, enzymes in recombinant and native systems
- *In vivo* Pharmacology (rodent and NHP)
  - CNS efficacy models
  - Drug addiction models
  - Stress-related models
  - Sleep-related model
  - PharmacoeEG studies
  - Feeding models
- Translational Biology
  - Receptor occupancy and PK/PD studies
  - Microdialysis
  - Target distribution
  - MRI Imaging
  - PET tracer characterization and development

- Biomarker analysis
  - Acute stress markers
  - Inflammation markers
  - Metabolic markers and adipokines
  - Hypothalamic neuroendocrine markers
  - Neuroplasticity markers
  - Sex hormones
  - Toxicity biomarkers (e.g. cardiac, kidney, hepatic)

##### Safety Pharmacology

- Electrophysiological technologies
  - Liability/selectivity panel
  - Cardiac safety panel
  - Manual patch-clamp
  - Potential for pro-convulsant liability evaluation
- *In vivo* models
  - CV *in vivo* telemetry
  - Echocardiography
  - Neuro-Cardio models
  - Anaesthetised models
  - Neurobehavioural tests (Irwin, FOB)
  - Pro-convulsant potential
  - Video-tEEG
  - Rotarod/motor coordination and spontaneous LMA
  - Abuse Liability assessment

##### DMPK

- *In vitro* Studies
  - Metabolic stability, tissue binding and distribution, interspecies profiling
- ADME Studies
  - Pharmacokinetics, mass balance, tissue distribution
- Mechanistic PK/PD analysis



#### DMPK (continued)

- High throughput
- Metabolic stability
- Drug interactions (enzymes and transporters)
- Permeability
- Plasma, blood and other tissues binding
- Bioactivation
- Non-clinical *in vivo* pharmacokinetics
- Detailed Metabolite Profiling and Identification – MIST
- Interspecies scaling and mechanistic PK/PD modelling

#### Bioanalysis

- Laboratory GLP accredited
- Preclinical GLP bioanalytical support
- High throughput sample analysis
- Dried Blood Spot technology
- High sensitivity method development and validation
- Clinical Support Services - Support for Phase I, II, III and IV
- Fast sample analysis turnaround (<48 hours for FTIH studies)

#### Toxicology and Pathology

- Early screening of toxicity, including *in silico* prediction
- Liability Assessment of biological targets
- Regulatory toxicity studies (GLP) up to 6 months
- Investigative and problem solving studies
- Integrated investigative capabilities, including biomarkers identification and validation
- Integration of Safety Pharmacology endpoints in General Toxicity studies
- Regulatory and Investigative Pathology, including electromicroscopy (GLP)
- Non Clinical Assessment of Safety and regulatory document preparation

#### Medicinal Chemistry and Computational Chemistry

- Lead Generation
- Lead Optimization
- Parallel multi-parameters optimization
- Chemical series exploration (design and/or synthesis)
- Hit and lead explosion using parallel synthesis
- Structure-activity relationship determination
- Lead series identification through Fast-follower approach

#### Clinical Sciences

- Design and implementation of clinical plans up to Phase II
- Design, management, analysis and interpretation of clinical pharmacology studies
- Design, management, analysis and interpretation of Phase II clinical studies
- Statistical analysis and interpretation
- Clinical Pharmacokinetic analysis and interpretation
- Pharmacometrics services
- Modelling and Simulation
- Translational and Experimental Medicine
- Medical governance

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**Engineering a better drug development  
process through scientific excellence.**