Discovery Research

Integrated Drug Discovery Capabilities

Discovery Research
Suven Life Sciences Ltd
Serene Chambers, Road-5, Avenue-7, Banjara Hills,
Hyderabad-500034, India.
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Overview

Suven Life Sciences

Vision & Mission

Vision

Search for new CNS therapies

Become the leading company focused on the treatments for unmet medical need in Mental Health

Mission

Health for Patients and Value for Partners

Excellent Pipeline of CNS drugs for Cognition, Depression and Pain
Novel Mechanism of action and first in class preclinical data

Clinical Candidates

SUVN-502, SUVN-G3031, SUVN-D4010 and SUVN-911

Suven Life Sciences

28 years of Pharmaceutical Leadership

1989
Incorporated by Mr. Venkat Jasti
1995
IPO, Listed on NSE and BSE in India

1989
Contract Research & Manufacturing Services (CRAMS)
FDA Approved Plant
(Handled more than 500 projects)

2002
Suven Discovery
(Cognition, Psychosis, Anxiety, Depression, Pain, Obesity, GI disorders)

2005
Drug Discovery & Development Support Services (DDDSS)
Major Pharma & Biotech (USA, Europe)

2006
Collaborative Research Program
Eli Lilly, USA

2009
Formulation Development
Clinical Trial Supplies

2013
First US IND for SUVN-502
2015
First Clinical Proof-of-Concept Study in USA for SUVN-502

Relationship with many (~30) Global Life Science and Biotech companies

Suven Life Sciences

Multi Location Facilities

Vizag, Andhra Pradesh, India
SUVEN API Facility

- 307 KL reactor volume
- 3KL to 12KL Reactors
- GL/SS (45No's)
- API's/Advanced Intermediate's/CMO

Pashamylaram, Hyderabad, India
SUVEN Discovery, API & Formulation Facility

- Discovery Research
- 120 kL reaction volume
- 50L – 6000 L GL/SS (45)
- API Manufacturing
- Biopharmaceutical Research (GLP)
- Formulation R&D

Banjara Hills, Hyderabad, India
Corporate Office

Jeedimetla, Hyderabad, India
SUVEN Discovery & Pilot Plant

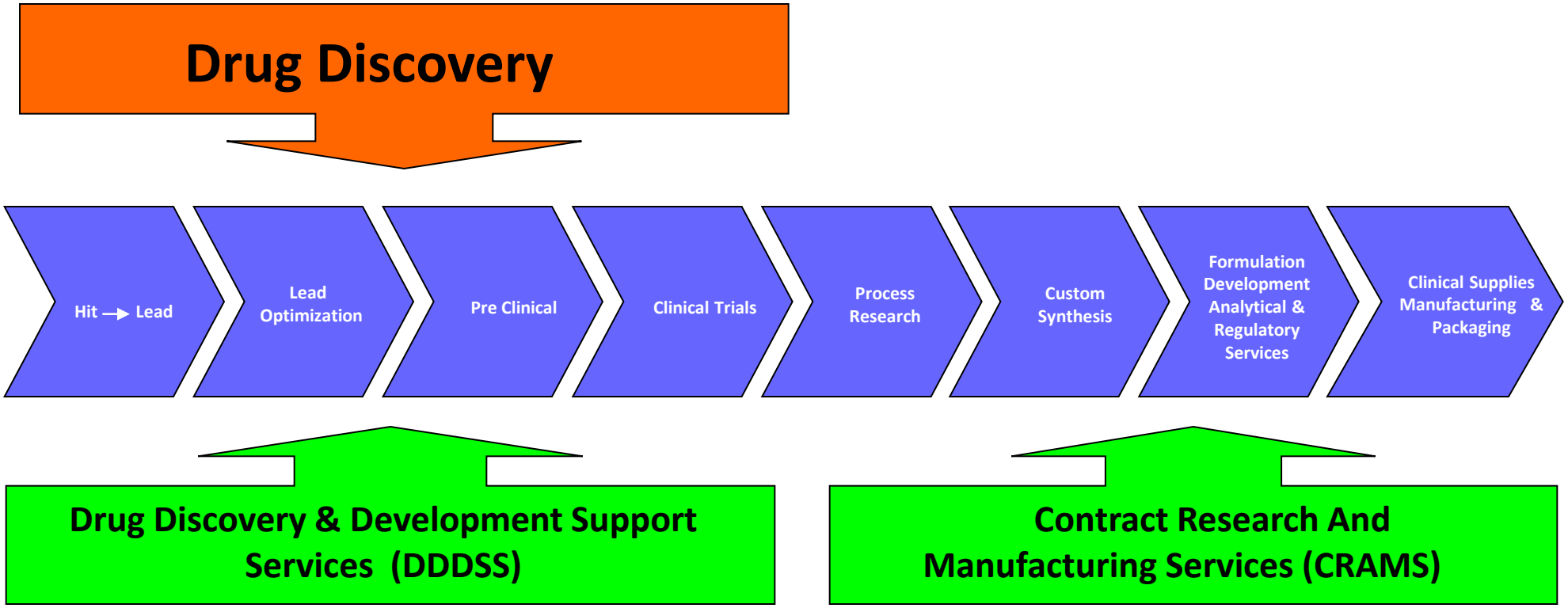
- Process Research
- Discovery R&D, Analytical R&D
- Killo lab, 30L CM Reactors (32)
- 50L – 4000 L GL/SS

Suryapet, Telangana, India
SUVEN Intermediate Mfg. Facility

SUVEN USA, New Jersey
Business Office

- Business Development
- Project Management
- Intellectual Property Management

Suven Business Model



Collaborative Research Partner (CRP) …

Seamless transition

Suven Discovery

Profile

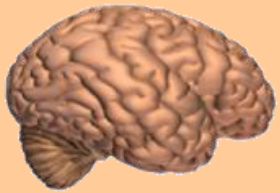
- Fifteen years of drug discovery and development experience
  - Working on 8-10 central nervous system targets in drug discovery
  - First discovery project delivered SUVN-502 (5-HT_6 receptor antagonist for Alzheimer's Disease). Phase II POC for Alzheimer's Disease in aged population is currently ongoing in USA
  - Three more internally discovered molecules (SUVN-G3031, SUVN-D4010 and SUVN-911) are currently being evaluated in human clinical trials

Suven Discovery

Core Research Area - Neuroscience

Suven discovery is focused on neuroscience, the most challenging area in drug discovery

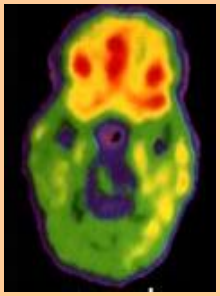
Alzheimer's Disease (AD)



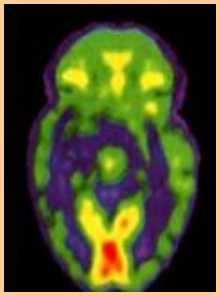
Normal Brain

Brain with AD

Schizophrenia

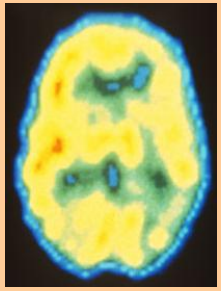


Normal Brain

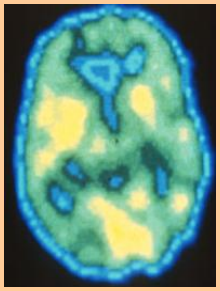


Schizophrenic

Depression



Normal Brain



Depressed

Research aim is to develop differentiated therapeutics for the treatment of neurodegenerative disorders

Suven Discovery

Therapeutic Targets

Alzheimer's Disease

- Symptomatic treatment
  - 5-HT_6 receptor antagonist
  - Histamine H_3 receptor inverse agonist
- Symptomatic and disease modifying treatment (dual mode of action)
  - 5-HT_4 receptor partial agonist
  - M1 receptor positive allosteric modulator (M1 PAM)

Schizophrenia

- Dopamine D_2, 5-HT_{2A}, 5-HT_{1A}, SSRI (Multimodal Project)
- M4 PAM
- Dual M1/ M4 agonist

Depression

- Nicotinic acetylcholine α4β2 receptor antagonist

Pain

- P2X7 antagonist

Gastro-Intestinal Motility Disorders

- 5-HT_4 agonist

Focused research with diverse mechanisms for multiple therapeutic areas

Suven Discovery

NCE Clinical Pipeline (4 US INDs)

Candidates	Pre-clinical & GLP Tox	Clinical Phase			Indication
		I	II	III	
SUVN-502 5-HT_6 antagonist					**Alzheimer's Disease**
SUVN-G3031 H_3 inverse agonist					**Cognitive Disorders** **Sleep Disorders**
SUVN-D4010 5-HT_4 agonist					**Cognitive Disorders**
SUVN-911 α4β2 antagonist					**Major Depressive Disorders**
SUVN-I6107 M1 PAM					**Cognitive Disorders**

SUVN-502
Phase II POC Study Currently Ongoing in USA (NCT02580305)

SUVN-G3031
Completed Phase I Clinical Trial in 2016 (NCT02342041, NCT02881294)

SUVN-D4010
Completed Phase I Clinical Trial in 2017 (NCT02575482, NCT03031574)

SUVN-911
Completed Phase I Clinical Trial in 2018 (NCT03155503)

Suven Discovery

NCE Research Pipeline

Program	NCE Profile	Indication
Multimodal (Dopaminergic and seretonergic receptor modulator)	• Potent, orally bioavailable with excellent brain penetration • Robust efficacy in various animal models of psychosis and depression • Modulation of dopamine, norepinephrine in cortex • Good margin of safety; Separation from motor side effects	**Psychiatric Disorders**
5-HT_4 agonist	• Potent, selective, non-brain penetrant • Clean cardiovascular safety profile • Potential to treat serious GI motility disorders	**Gastro-Intestinal Motility Disorders**
M4 PAM	• Hit to Lead stage	**Psychosis**
Dual M1/ M4 agonist	• Hit to Lead stage	**Cognition and Psychosis**
P2X7 antagonist	• Hit to Lead stage	**Pain and Inflammation**

Suven Discovery

Patent Portfolio

PCT and National Phase	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	Total
Applications	1	8	4	3	2	3	3	4	4	1	2	1	5	-	6	4	-	51
Published	-	3	7	3	1	5	3	2	2	5	2	1	2	2	5	4	4	51
National Phase entered	-	-	3	3	1	1	2	3	1	2	5	3	1	1	2	5	1	34

Suven Discovery

Patent Portfolio

Granted Patents	Europe	USA	Australia	Japan	Singapore	New Zealand	Israel	ARIPO
Composition of matter	25	28	30	23	27	28	13	3

	South Africa	India	Sri Lanka	Korea	Brazil	Mexico	Macau
Composition of matter	23	28	13	23	2	22	10

	Canada	China	Eurasia	Norway	Hongkong	Russia
Composition of matter	26	22	22	9	23	3

Suven Discovery

Published PCT Patent Applications

Year	Publication Numbers	Number of Publications
2018	WO 2018/033847, WO 2018/033848, WO 2018/042362, WO 2018/065869	4
2017	WO 2017/042643, WO 2017/199070, WO 2017/199071, WO 2017/199072	4
2016	WO 2016/027275, WO 2016/027276, WO 2016/027277, WO 2016/128990, WO 2016/198937	5
2015	WO 2015/083179, WO 2015/092804	2
2014	WO 2014/030170, WO 2014/147636	2
2013	WO 2013/042135	1
2012	WO 2012/029070, WO 2012/114348	2
2011	WO 2011/030349, WO 2011/061751, WO 2011/080751, WO 2011/080750, WO 2011/083487	5
2010	WO 2010/032257, WO 2010/032258	2
2009	WO 2009/034581, WO 2009/053997	2
2008	WO 2008/084492, WO 2008/084491, WO 2008/136017	3
2007	WO 2007/020653, WO 2007/020652, WO 2007/046111, WO 2007/046112, WO 2007/138611	5
2006	WO 2006/095360	1
2005	WO 2005/066184, WO 2005/066157, WO 2005/005439	3
2004	WO 2004/108671, WO 2004/055026, WO 2004/048331, WO 2004/048330, WO2004/048328, WO 2004/041781, WO 2004/083202	7
2003	WO 2004/000849, WO 2004/000845, WO 2004/000205	3
	Total as on Apr 2018	**51**

Suven Discovery

Publications

More than 100 publications indexed in PubMed covering Medicinal chemistry, ADME and pharmacokinetics, Behavioral pharmacology, Neurochemistry and biomarkers, Bioanalysis, Safety pharmacology and Toxicology

Journals	Impact factor
Medicinal Chemistry	
Journal Of Medicinal Chemistry	5.44
European Journal of Medicinal Chemistry	3.44
ACS Medicinal Chemistry Letters	3.12
Bioorganic & Medicinal Chemistry Letters	2.42
Journal of Enzyme Inhibition and Medicinal Chemistry	2.33
Pharmacology	
Behavioural Brain Research	3.02
European Journal Of Pharmacology	2.53
Journal Of Pharmacological And Toxicological Methods	2.39
Behavioural Pharmacology	2.14
Journal Of Neuroscience Methods	2.02
Pharmacological Reports	1.92

Journals	Impact factor
ADME & Pharmacokinetics	
Drug Metabolism and Disposition	3.25
Chemico-Biological Interactions	2.57
Xenobiotica	2.19
Analytical Techniques	
Journal Of Pharmaceutical And Biomedical Analysis	2.97
Journal of Chromatography B: Biomedical Sciences and Applications	2.72
Biomedical Chromatography	1.72
Toxicology	
Drug And Chemical Toxicology	1.23
Lab Animal	0.74

Suven Discovery

Conferences

More than 10 years of participation and scientific data presentations at

- Society of Neuroscience (SfN, USA)
- Alzheimer's Association International Conference (AAIC, USA/ Europe/ Canada)
- Clinical Trials on Alzheimer's Disease (CTAD, USA/ Europe)
- American Association of Pharmaceutical Scientists (AAPS, USA)
- International Society for the Study of Xenobiotics (ISSX , USA/ Europe)
- American Chemical Society (ACS, USA)
- Society of Toxicology (SOT, USA)
- Safety Pharmacology Society (SPS , USA/ Europe/ Canada)
- Controlled Release Society (CRS , USA/ Europe/ Canada)
- Applied Pharmaceutical Analysis (APA, USA/ India)
- Indian Pharmaceutical Congress (IPC, India)
- Annual meeting of Society for Neurochemistry (SNCI, India)
- National Conference on Ethical Use of Animals in Research & Education and Disseminations of Norms & Guidelines of CPCSEA (India)

5 to 10 scientists from different discipline attend and present their research work every year

Suven Discovery

Training Programs

- Lilly research laboratories (USA)
- Bristol-Myers Squibb (USA)
- Karolinska Institute (Sweden)
- Data Sciences International (USA)
- Cambridge Electronic Design (USA)
- Basic LC-MS-MS Training, Applied Bio-Systems (Germany)
- Training on electrophysiology & Nanion's Patchliner instrument (Germany)
- Hands-On workshop: Introduction to Phoenix WinNonline and PK/PD (India)
- Bureau of Indian Standards (BIS) - Laboratory Quality System, Management & Internal Audit as per ISO/IEC 17025 (India)
- Training course on radiological safety (BARC, India)
- Practical chiral HPLC method development training course (India)
- Gastro Plus Simulation and Modeling workshop (India)

Suven Discovery

Collaboration Objectives

- To innovate and discover clinically developable drug candidates through Collaborative Research by developing and demonstrating full spectrum Discovery and Development Capabilities

- To provide collaborative Drug Discovery & Developmental Support in Medicinal chemistry, Process chemistry, Analytical chemistry, Assay development, *In-vitro* Screening, ADME, Receptor Occupancy, CNS (Anxiety, Cognition, Psychosis, Depression), Pain and Obesity Pharmacology, Microdialysis, EEG, Discovery Toxicology, Safety, Formulation Development & Bio-analysis

Suven Discovery
CNS Collaborative Experience with Global Companies

Collaborative Research Partnership in 2006 with Eli Lilly

- Two full spectrum Discovery Collaborative Projects:
- **First project:** CNS target - Hit to Candidate Identification
- **Second Project:** Dual CNS Target Pharmacology involving Hit Identification to Candidate Selection over a period of 3 years and then to GLP tox and clinical development .
- Target engagement and tracer identification for novel targets

Collaborative Research Partnership with Prexa and Reviva (USA)

- Lead Optimization to Candidate Selection : From in-vitro screening to non-clinical safety assessment

Collaborative Research Partnership with a Big Pharma (USA)

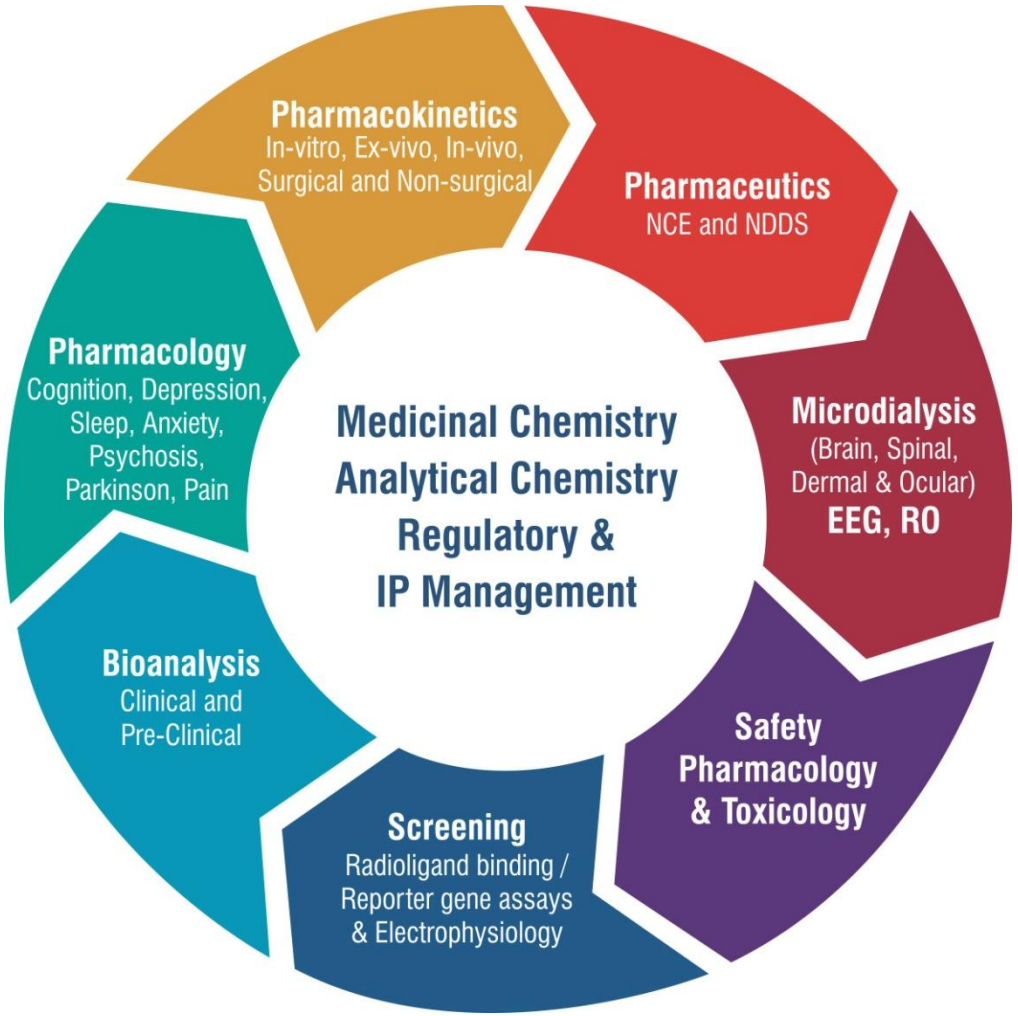
- Candidate selection using behavioral assays
- Target engagement and tracer identification for novel targets

Suven Discovery

Research Partners

Suven Discovery

Key Infrastructure



Full Spectrum Drug Discovery and Collaborative Research

Suven Discovery

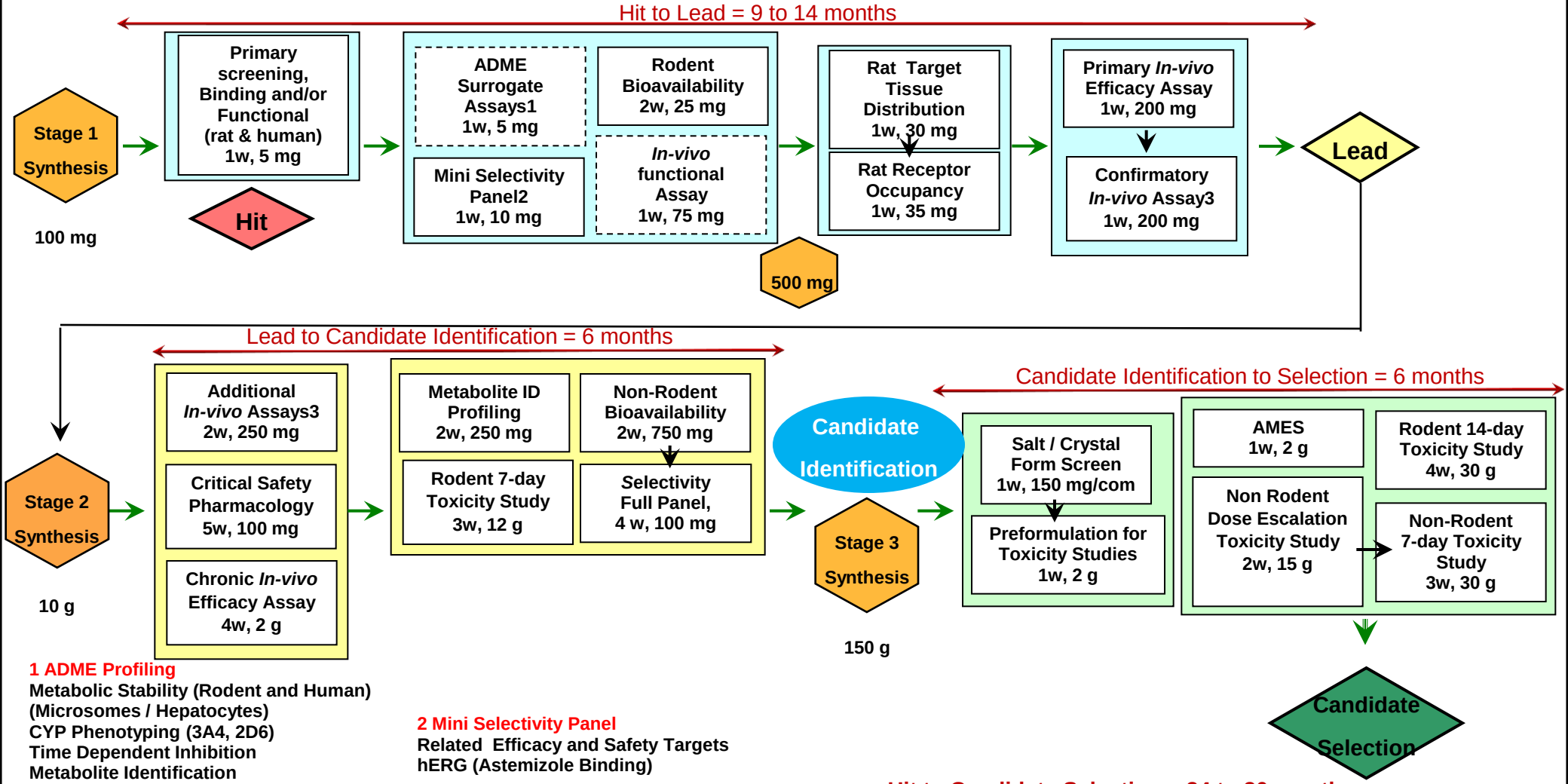
Scientists Qualifications / Experience

	Scientists Breakdown				
	Ph.D.	Average Years Experience	MS / M.Pharm	Average Years Experience	Technician / Lab Support
Chemistry	10	>15 Years	50	2 - 6 years	12
Biology	12	>12 Years	65	2 - 8 years	25
DMPK	7	>14 Years	45	2 - 5 years	12
Management	1 (>25 years of discovery experience)				
Office / Admin	25				

Senior and Core Group Leaders have pursued their education from reputed academic institutions like **IIT** (Indian Institute of Technology), **IISc** (Indian Institute of Science**),** **IICT** (Indian Institute of Chemical Technology), Osmania University, Manipal University, MS University Baroda, LM College of Pharmacy, Hyderabad Central University etc.

Suven Discovery

Discovery Flow Scheme (Hit – Lead – Candidate)



1 ADME Profiling
Metabolic Stability (Rodent and Human) (Microsomes / Hepatocytes)
CYP Phenotyping (3A4, 2D6)
Time Dependent Inhibition
Metabolite Identification
In-vitro CaCO2 Permeability

2 Mini Selectivity Panel
Related Efficacy and Safety Targets
hERG (Astemizole Binding)

Hit to Candidate Selection = 24 to 30 months

Suven Discovery

Data Communication

Collaborative Projects

- Data upload in dedicated eRoom on real time
- Secured Tunnel for safe email exchanges
- Weekly WebEx for Chemistry, Biology and project progression
- Regular teleconference with the collaborative partners
- Access to structures is restricted

Internal Projects

- Secured tunnel for email exchanges between different divisions
- Internal project progress meeting for Chemistry and Biology
- All compound related communications with internal Suven code numbers
- Access to structures is restricted

Suven Discovery

Medicinal Chemistry

Core Capabilities

- Hit generation and follow up
- Independent or collaborator supported hit to lead and lead optimization with consideration of potential IP issues
- Lead optimization and selection of clinical development candidate
- Salt selection and polymorph screening
- Identification, synthesis and characterization of metabolites
- Synthesis of reference standards
- Access to STN, Sci-Finder and major scientific journals
- Scale-up chemistry support
- Dedicated analytical support laboratory
- Dedicated and experienced intellectual property management team

Suven Discovery

Medicinal Chemistry

Core Strength - The People

- Highly qualified, experienced and committed Scientists
- Well versed with Medicinal & Contemporary Chemistry
- Experience span across a wide range of chemistry skill sets
- Advanced knowledge in IP issues, highest level of confidentiality
- Well acquainted with GLP & safety practices
- Trained for data mining and literature searches

Labs and Facilities

- Spacious and well equipped air conditioned laboratories
- Integrated write up area and IP secure areas within the lab for scientists
- Advanced purification systems like Combiflash
- Non-conventional synthesis equipments like Microwave synthesizer
- Separate hydrogenation laboratory (Capacity 100 mL to 5 L)
- Highly organized chemical inventory store
- Expertise and infrastructure to handle high pressure, high temperature/cryogenic reactions

Suven Discovery

Medicinal Chemistry and Analytical Labs

Chemistry Manufacturing and Control

- Dedicated Scientists with good experience in scale up and manufacture
- Excellent Kilo lab and FDA approved production facilities
- Expertise in route selection and process controls (crystallization and polymorph control)
- Competitive time lines and speedy delivery with quality
- Demonstrated CMC capabilities in production of our Phase 2 clinical candidate SUVN-502 on 75 Kg scale at FDA approved plant. Other Phase 1candidates (SUVN-G3031, SUVN-D4010 and SUVN-911) were scaled up at ~5-10 kg level

Analytical Facilities

- 400 MHz NMR (Bruker) with three different probes – dual, multinuclear and fluorine
- Dedicated mass spectrometer for Med Chem - LC MS/MS API-2000 (Applied biosystems)
- Several Agilent HPLC systems with UV, PDA, Fluorescence and RI detectors
- One Agilent GC system with head space and FID detector
- Semi-preparative scale chromatographic systems
- Polarimeter, DSC, TGA, UV spectrophotometer and FTIR

Suven Discovery

Medicinal Chemistry and Analytical Labs






Suven Discovery

In Vitro Biology

Expertise	A group of dedicated scientists with overall expertise in Biochemistry, Molecular Biology and Cell Biology
Drug target class	Encompassing drug target class: GPCRs, Nuclear Receptors, Monoamine transporters, ion channels and enzymes
Proficiency	Assay Development and Validation, Screening and Profiling of Compounds, and Diverse Mechanistic Studies of Lead/ Lead Like Molecules

Suven Discovery

Protein Expression, Purification and Interaction

Cloning And Expression

- Human cDNA Synthesis and Cloning
- Expression of Recombinant Proteins in *E. coli*, Baculovirus and Mammalian Cells

Protein Purification

- Purification and Characterization of Recombinant Proteins using affinity tag

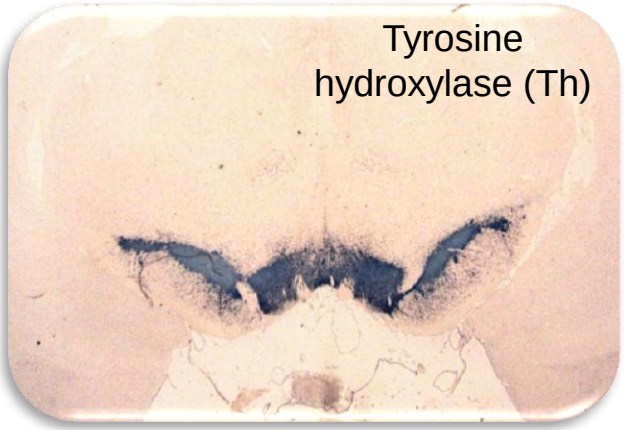
Protein – Protein Interactions

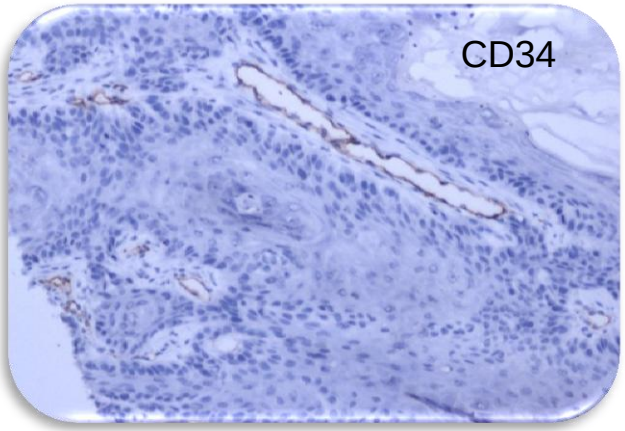
- Yeast Two-Hybrid System and other yeast based assays
- His Tag Pull Down

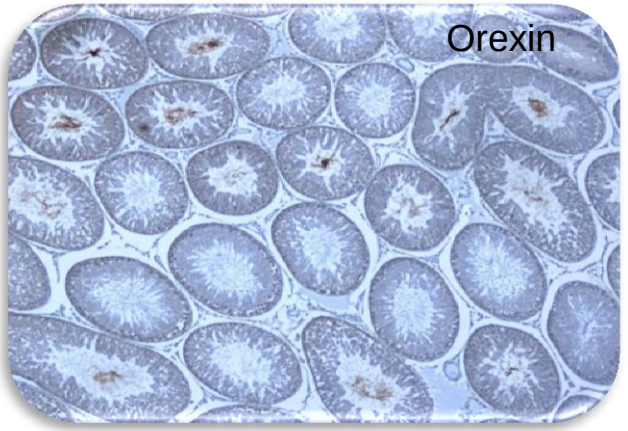
Suven Discovery

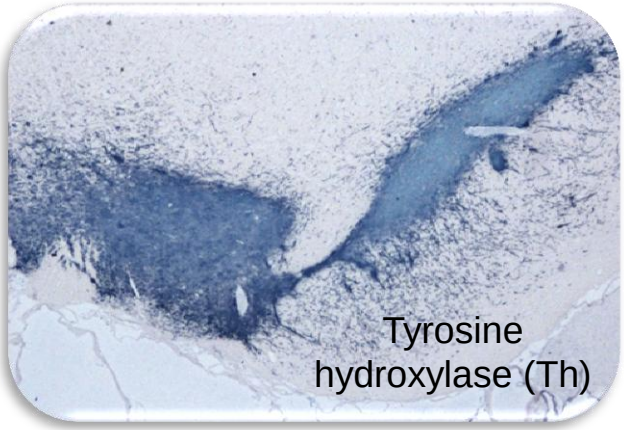
Protein Localization

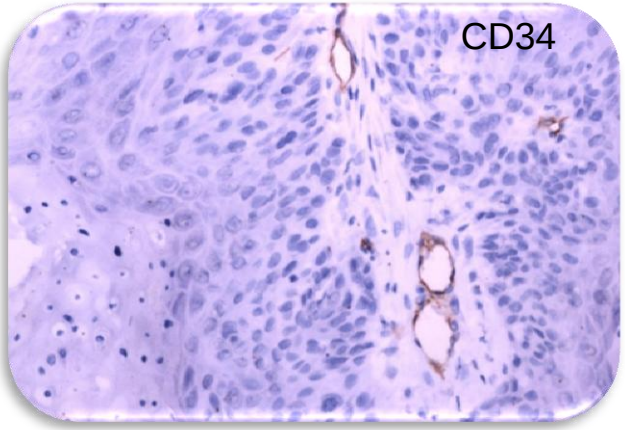
Protein Localization - Immunohistochemistry

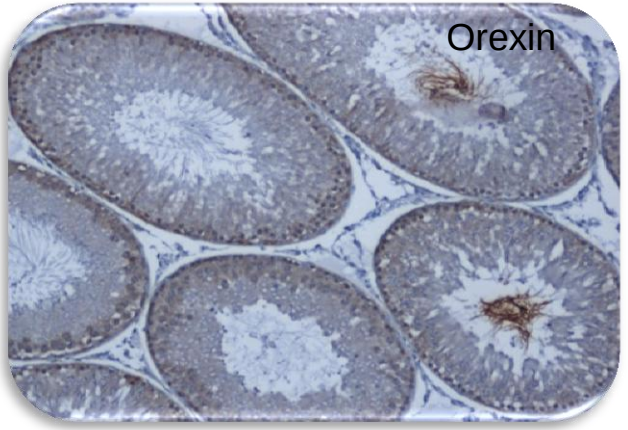












Suven Discovery

Cell line and Cell culture

Cell Bank

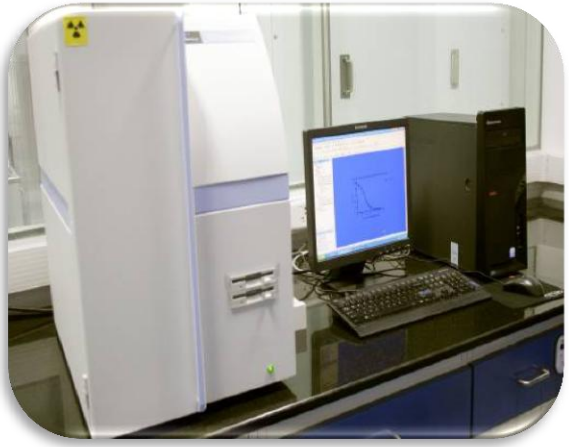
- CHO-K1, HEK293, IMR32, Caco-2, Sf9, HepG2, U-937, and PC12

Recombinant stable cell line generation

- Stable cell line are primary source for cell based assays and membrane proteins for binding assays
- Recombinant stable cell lines were generated in CHO-K1/ HEK293 parent cell line using recombinant expression construct and CRE-Luc reporter by liposomal transfection
- Pure clones were identified by single cell per well dilution
- Validated using reference agonist and antagonist dose response

Suven Discovery

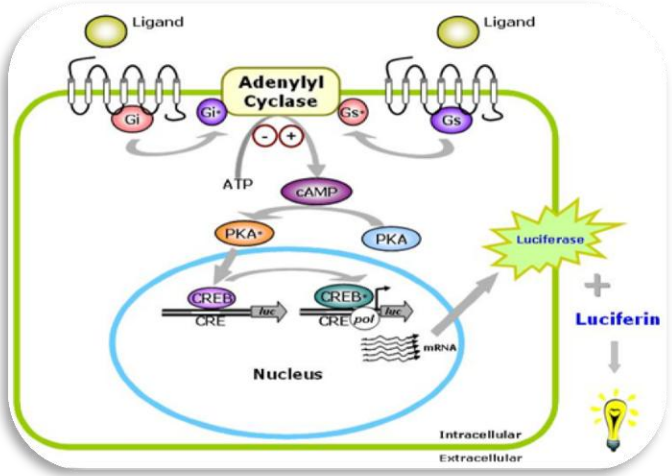
Radio-ligand Binding Assays



- Atomic Energy Regulatory Board of India (AERB) approved facility
- Validated binding assays from target class GPCRs, Ion channels and Transporters
- Validated Functional uptake assays for monoamine transporters
- Scintillation Proximity Assay (SPA) bead and filtration based platform

Suven Discovery

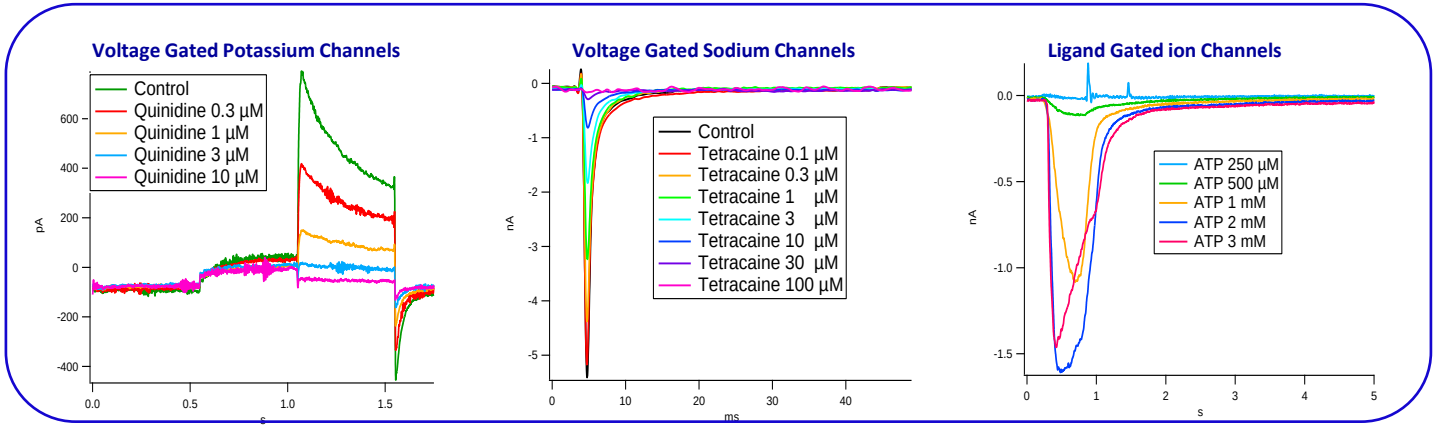
Cell Based Assays



- Validated cell lines were used for screening compounds along with reference compounds in each plate
- Luciferase reporter gene based assay was utilized to determine functionality of compounds representing various class with varying affinities
- EC_{50}, IC_{50}, and K_b values were derived
- Agonist, Antagonist and allosteric modulators can be identified

Suven Discovery

In Vitro Electrophysiology Assays



- Versatile automated Patch clamp assays for both Voltage gated and Ligand gated ion channels using Nanion Patch clamp instrument
- Patch clamp assays for temperature sensitive receptors like TRPV1, hERG etc can be measured at ideal temperatures with inbuilt temperature control system
- Validated assays for safety profiling and screening therapeutic targets like pain and other CNS disorders
- Voltage gated ion channels - Potassium channels **K_v 10.1(eag1), K_v 11.1(hERG);** Sodium channels **Na_v 1.4, Na_v 1.5, Na_v 1.6, Na_v 1.7**
- Ligand gated ion channels - Purinergic receptors **P2X7**

Suven Discovery

List of *In Vitro* Assays

Target	Assay Type
GPCRs	
Adenosine A_{2A}	Reporter gene driven cell based
Adrenoceptor α_{1B}	Reporter gene driven cell based/ Radioligand binding
Adrenoceptor α_{2C}	Reporter gene driven cell based
Serotonin 5-HT_{1A}	Reporter gene driven cell based/ Radioligand binding/ β-arrestin
Serotonin 5-HT_{2A}	Reporter gene driven cell based/ Radioligand binding/ β-arrestin
Serotonin 5-HT_{2C}	Radioligand binding
Serotonin 5-HT_{4}	Reporter gene driven cell based/ Radioligand binding
Serotonin 5-HT_{6}	Reporter gene driven cell based
Serotonin 5-HT_{7}	Reporter gene driven cell based/ Radioligand binding
Dopamine D_1	Reporter gene driven cell based
Dopamine D_2	Reporter gene driven cell based/ Radioligand binding/ β-arrestin
Dopamine D_3	Radioligand binding
Dopamine D_5	Reporter gene driven cell based
Histamine H_1	Reporter gene driven cell based/ Radioligand binding

Suven Discovery

List of *In Vitro* Assays

Target	Assay Type
GPCRs	
Histamine H_3	Reporter gene driven cell based
Histamine H_4	Reporter gene driven cell based/ Radioligand binding
Muscarinic M_1	Reporter gene driven cell based/ Radioligand binding/ β-arrestin/ IP1 assay
Muscarinic M_2	Reporter gene driven cell based/ Radioligand binding
Muscarinic M_3	Reporter gene driven cell based/ Radioligand binding
Muscarinic M_4	Reporter gene driven cell based/ Radioligand binding
Muscarinic M_5	Reporter gene driven cell based/ Radioligand binding
Cannabinoid CB_1	Reporter gene driven cell based
Cannabinoid CB_2	Reporter gene driven cell based/ Radioligand binding
Prostaglandin EP2	Reporter gene driven cell based
Transporters	
SERT	Radioligand binding/ Functional uptake
DOPT	Radioligand binding/ Functional uptake
NET	Radioligand binding/ Functional uptake

Suven Discovery

List of *In Vitro* Assays

Target	Assay Type
Nuclear receptors	
LXR alpha	Reporter gene driven cell based
LXR beta	Reporter gene driven cell based
RXR alpha	Reporter gene driven cell based
PXR	Reporter gene driven cell based
PPAR gamma	Reporter gene driven cell based
Ion Channels	
Nicotinic α4β2	Radioligand binding
Serotonin 5-HT_3	Radioligand binding
Potassium K_v 10.1	Electrophysiology
Potassium K_v 11.1 (hERG)	Radioligand binding/Electrophysiology
Sodium Na_v 1.4	Electrophysiology
Sodium Na_v 1.5	Electrophysiology
Sodium Na_v 1.6	Electrophysiology
Sodium Na_v 1.7	Electrophysiology
Purinergic P2X7	Electrophysiology

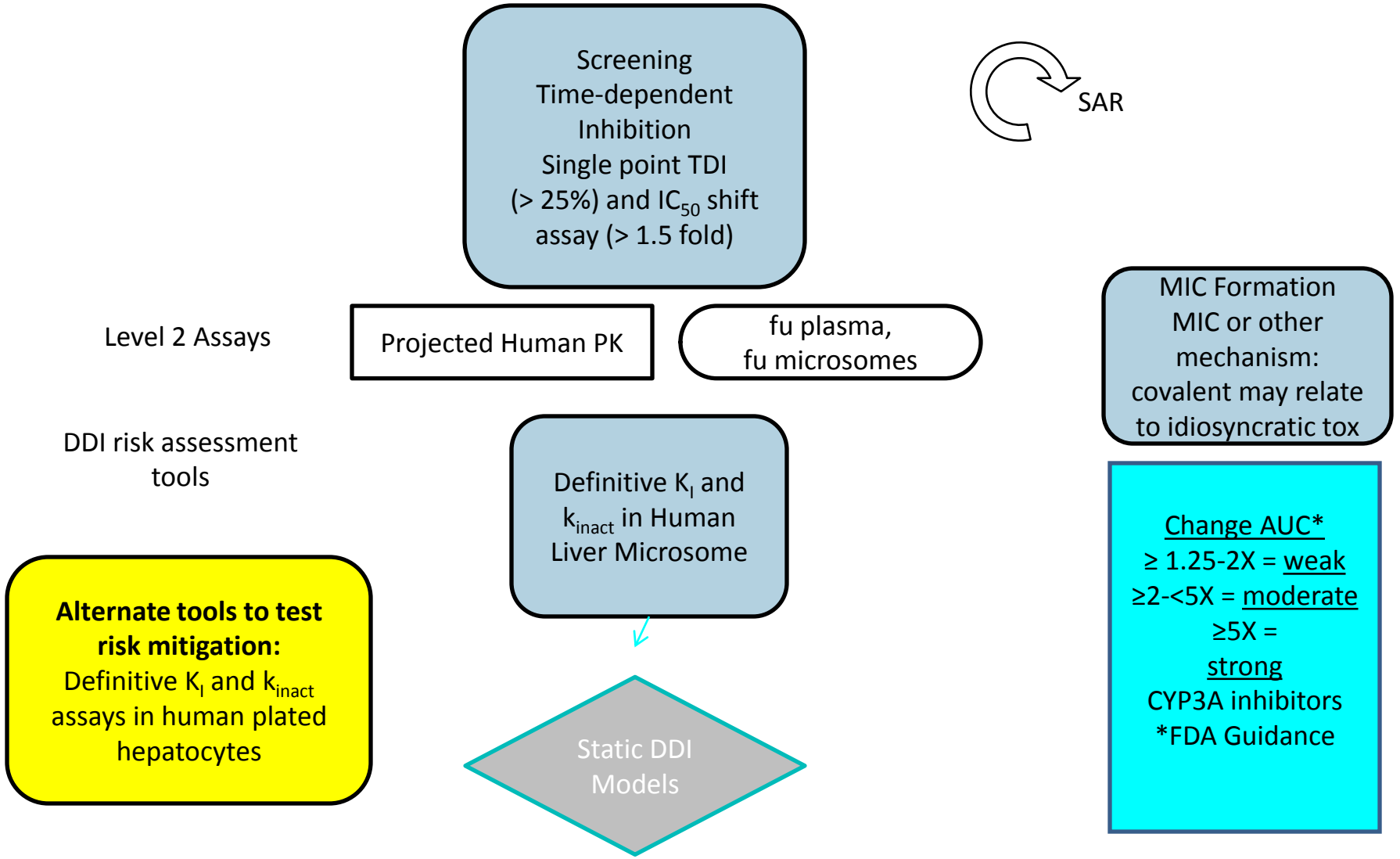
Suven Discovery

In Vitro ADME

Absorption	Solubility (Kinetic), Lipophilicity (LogD7.4), Permeability (PAMPA and Caco-2) and Efflux assays (Caco-2)
Distribution	Protein binding (plasma, brain homogenate, and microsomes) Blood to plasma partitioning (Species: rat, dog, and human)
Metabolism	Metabolic stability and intrinsic Clearance (S9, microsomes, rP450, hepatocytes), Reaction phenotyping (CYP and non-CYP, Enzyme kinetics, Chemical inhibition method and RAF), Metabolite identification and GSH trapping
Drug-Drug Interactions	Direct inhibiton (IC_{50} and Ki) Time dependent inhibition (Single point, IC_{50} shift, KI and Kinact, Dialysis) CYP Induction (mRNA expression and enzyme activity) Uptake transporters: substrate and inhibition assays (OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE-1 and MATE-2K)

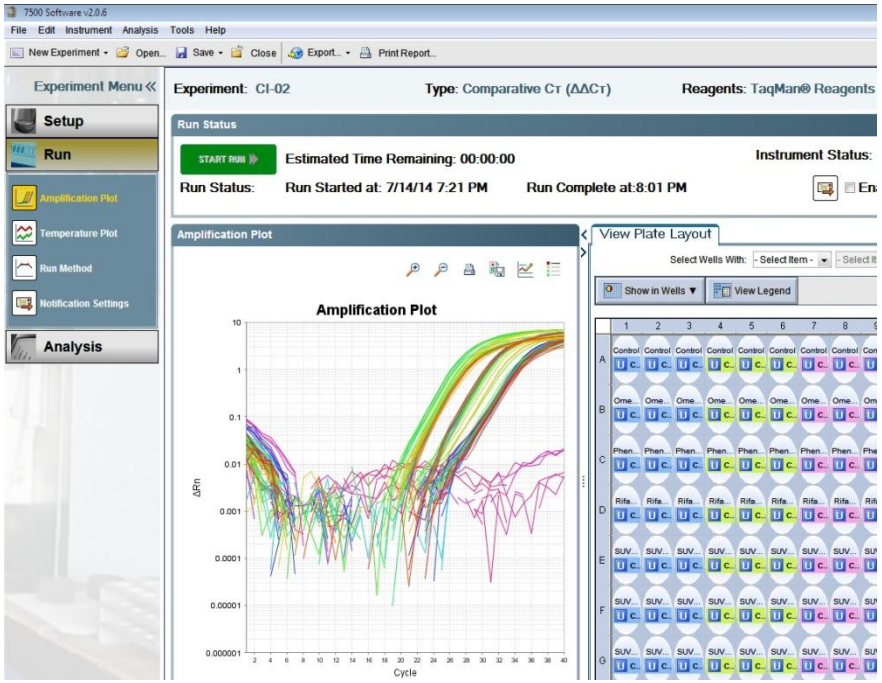
Suven Discovery

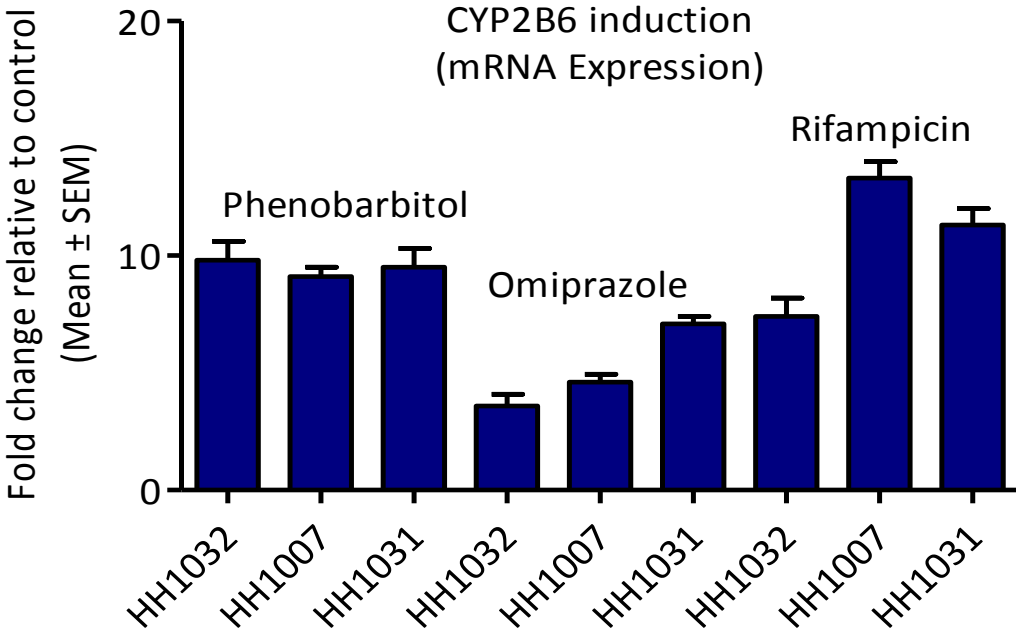
Time Dependent Inhibition



Suven Discovery

CYP Induction



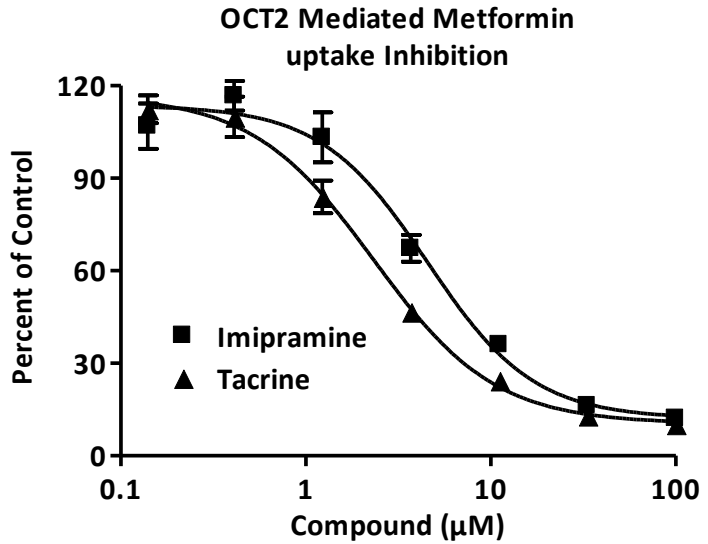


Lot # HH1032, Female, Age-68, Caucasian
Lot # HH1007, Female, Age-26, Caucasian
Lot # HH1031, Male, Age-42, Hispanic

Suven Discovery

Uptake Transporter (IC_{50} assay)

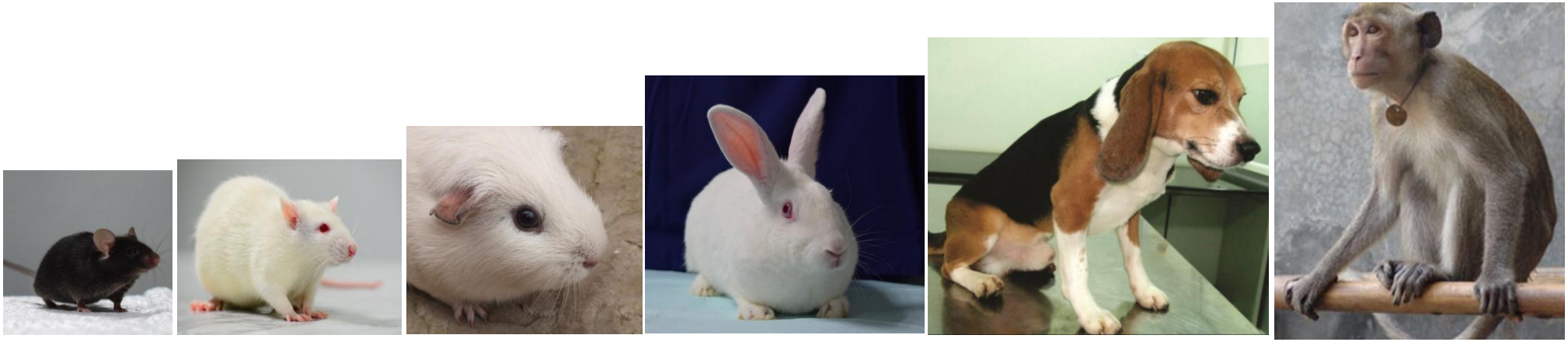
Transporter	Substrate	Positive control	Absolute IC_{50} (uM)
OAT1	Para-aminohippuric acid (PAH)	Flufenamic acid	0.5
OAT3	Estrone 3-sulfate (E3S)	Indomethacin	0.7
O CT1	Tetraethyl ammonium (TEA)	Verapamil	5.0
O CT2	Metformin	Imipramine	6.4
OATP1B1	Estradiol β-D Glucuronide	Sulfasalazine	3.4
OATP1B3	Estradiol β-D Glucuronide	Rifampicin	2.3



Compound ID	OCT2 Abs IC_{50} (µM)	Literature Reported
Imipramine	6.4	3.3
Tacrine	3.4	3.1

Suven Discovery

Animal Species for Pharmacokinetics



Mouse Rat Guinea pig Rabbit Dog Monkey

Small animals

Large animals

- **Oral**
  - Solutions, Suspensions, Films
- **Parenteral (Intravenous, subcutaneous infusions)**
  - Bolus, Continuous and Intermittent Infusion
- **Intranasal (Powders and Liquids)**
- **Ocular and Dermal**

Suven Discovery

In Vivo ADME

- Rodent bioavailability studies (Mouse, Rat, Guinea pig & Hamster)
- Intranasal and topical pharmacokinetic studies in rats
- Non Rodent bioavailability study (Rabbit & Beagle Dog)
- Site specific absorption studies in rats (Single pass In situ intestinal perfusion studies)
- Brain penetration studies (Total, discreet brain regions, Steady state brain penetration, In situ brain perfusion and CSF penetrations studies)
- Free drug estimation in brain using microdialysis
- Mouse brain uptake assay (MBUA)
- Disposition studies (Bile, Urine and Feces) using [3H] or [14C] ligands using LSA
- *In vivo* transporter mechanistic studies in rats
- *In vivo* approach for evaluation of MBI of CYP3A in rats
- PK/PD studies (exposure in plasma and brain)/ Allometric Scaling to predict human PK

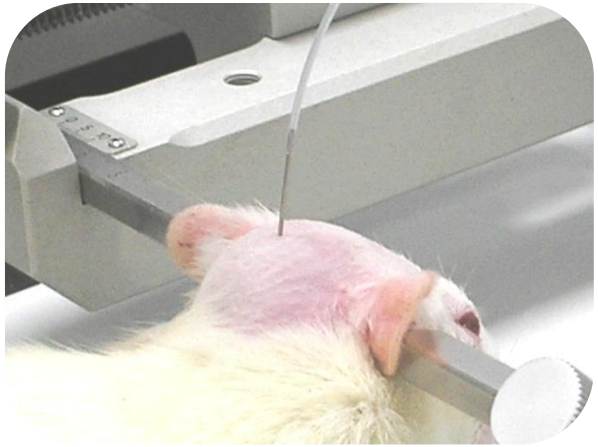
Suven Discovery

Surgical Models

- Jugular vein Cannulated Rats, Guinea pigs & Hamsters
- Femoral vein Cannulated Rat & Guinea pigs
- Portal vein Cannulated Rat and Guinea pigs
- Carotid artery Cannulated Rats
- Abdominal aorta Cannulated Rats
- Bile Duct Cannulated Rats
- Duodenal, Jejunum, Ileum and Colon Cannulated Rats
- CSF collection from rats
- Synovial fluid collection from rats

Suven Discovery

Assessment of CNS Penetration



Brain Penetration Studies

- Single dose
- Steady state

Collection of CSF

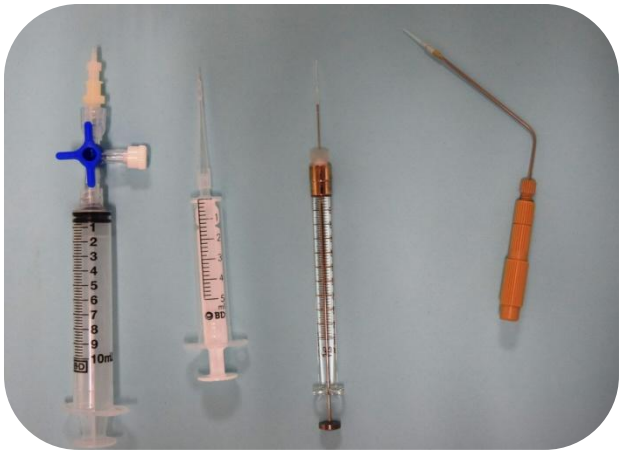
- Direct puncture of cisterna magna
- Species: Rat, Mouse, Rabbit, Dog

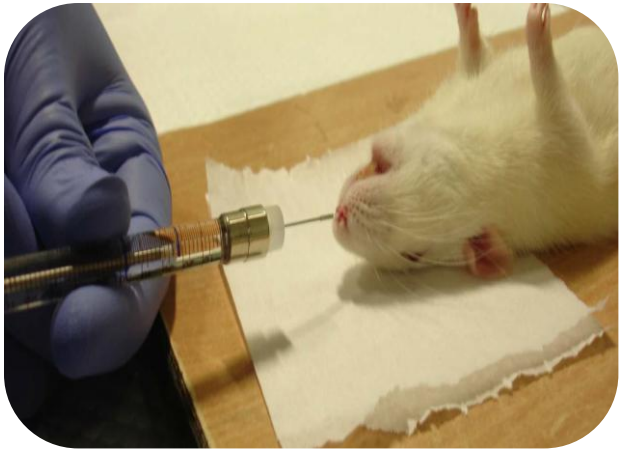
Brain Microdialysis

- Estimation of unbound concentration
- PK/PD assessment
- Species: Rat, Mouse, Rabbit

Suven Discovery

Specialized Drug Delivery





Products

- Solutions
- Powder

Advantages of Intranasal Delivery

- Delivery of drug directly to the brain
- Non-invasive, rapid absorption and amenable for biologics

Study Designs

- Single and multiple dose PK
- Cross-over study design

Suven Discovery

Receptor Occupancy, Radiolabelled/ Non-radiolabelled

Receptor Occupancy (RO) using Mass Spectrometry

- Method validated for > 25 targets
- High Throughout; Rapid turnaround time
- Simultaneous test compound monitoring
- Simultaneous Double/ Triple RO validated

RO using Liquid Scintillation Analyzer (LSA)

- Higher Specificity, Higher Sensitivity
- Suitable for Low Density Receptors

Infrastructure

- AERB Approved facility for handling radioligands
- Tricarb, MicroBeta TriLux

Methods

- *In vivo, ex vivo* receptor occupancy
- Transporter assays

Suven Discovery

Receptor Occupancy, Radiolabelled/ Non-radiolabelled

Receptor	Tracer
#, * **5-HT$_{1A}$**	WAY-100635■
5-HT$_{1B}$	AZ10419369
* **5-HT$_{2A}$**	MDL-100907
5-HT$_{2C}$	SB242084
5-HT$_{4}$	SB207145
5-HT$_{6}$	Lu AE60157■
NERT	S,S-MeNER
DAT	Nomifensine
#SERT	DASB
GABA$_{A}$	Flumazenil
CB$_{1}$	AM251

Receptor	Tracer
A$_{2A}$	SCH442416
nAChR α$_4$β$_2$	ZW-104
nAChR α$_7$	Methyllycaconitine
Histamine H$_3$	GSK-189254
PDE10	AMG 7980
D$_1$	SCH39166
* **D$_2$**	Raclopride■
NK1	GR205171
mGluR5	MPEPy
Adrenergic α1A	Prazosin

Receptor	Tracer
Sigma 1	FTC-146
MAO-A	Hamine
MAO-B	Selegiline

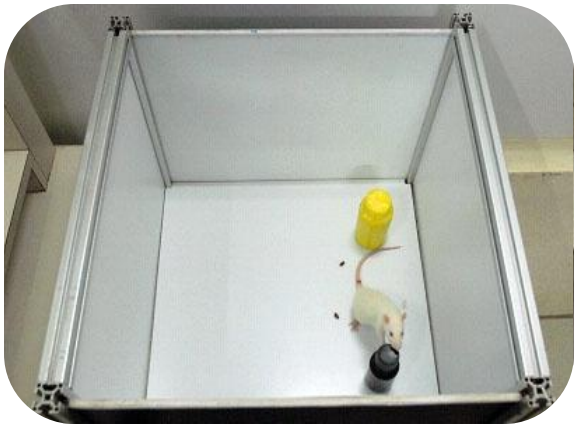
All tracer are non-radiolabelled tracers; ■ Radiolabelled tracers; *# Dual or triple target receptor occupancy assay

5-HT: Serotonin; NERT: Nor epinephrine reuptake transporter; DAT: Dopamine reuptake transporter; SERT: Serotonin reuptake transporter; GABA: Gamma amino butyric acid: CB: Cannabinoid; A: Adinosine; nAChR: nicotinic acetylcholine receptor; PDE: Phosphodiesterase; D: Dopamine; NK: Neurokinin; mGluR: metobotropic glutamate receptor

Suven Discovery

Rodent Models of Cognition

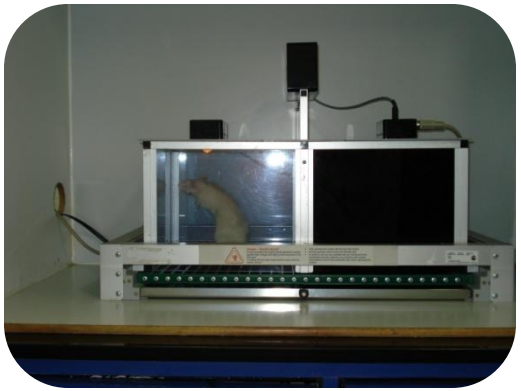
- Object recognition task
- Morris water maze
- Radial arm maze
- T-Maze
- Contextual fear conditioning
- Social recognition task
- Cerebral blood flow

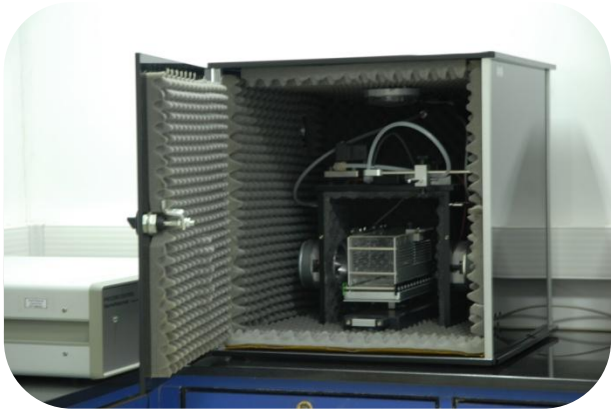


Suven Discovery

Rodent Models of Psychosis

Prepulse inhibition
MK-801 induced hyperlocomotion & stereotypy
Amphetamine induced hyperlocomotion & stereotypy
Condition avoidance response
Dominant submissive assay (Mania)
Resident intruder task

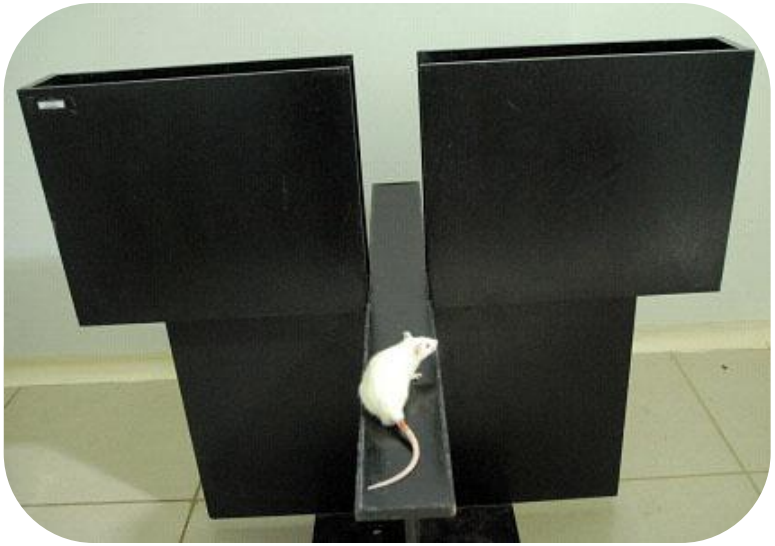


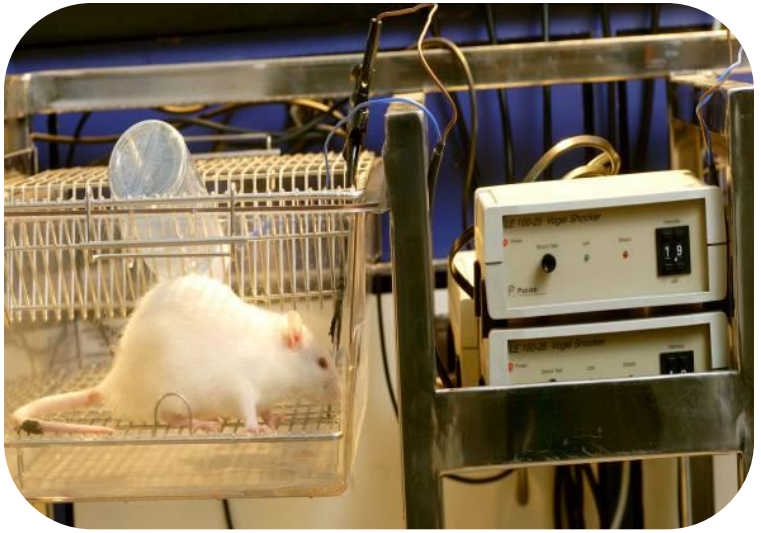


Suven Discovery

Rodent Models of Anxiety

Elevated Plus Maze
Vogel conflict test
Hole board
Novelty induced hypophagia





Suven Discovery

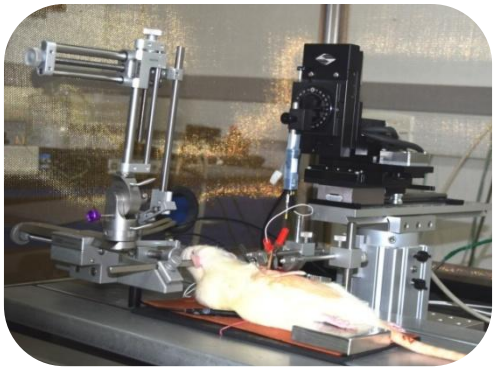
Rodent Models of Depression

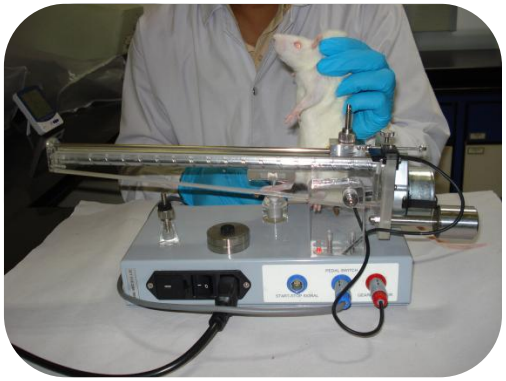
Forced swim test (Rat & Mouse)
Dominant submissive assay
DRL-72s
Tail suspension test

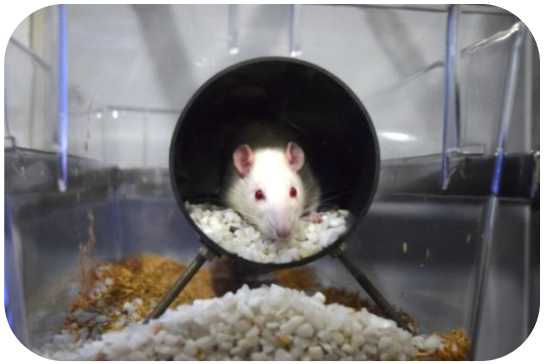
Suven Discovery

Rodent Models of Pain Disorders

Formalin Induced Nociception, Hot Plate & Acetic acid induced writhing
Complete Freund's Adjuvant - induced mechanical hyperalgesia
Chemotherapy - induced neuropathic pain
Streptozotocin - induced diabetic neuropathic pain
Spinal nerve (l5) ligation - induced neuropathic pain
Chronic constricted injury (CCI) - induced neuropathic pain
Partial sciatic nerve ligation (PSNL) -induced neuropathic pain
Capsaicin induced secondary mechanical allodynia in rats
Mono iodoacetate induced osteoarthritis
Complete freunds adjuvant induced rheumatoid arthritis
Medial meniscal tear model of osteoarthritis
Reserpine induced myalgia in rats
Chronic post-ischemia pain
Arachidonic acid induced ear odema
Spontaneous burrowing behavior in pain models
In vivo electrophysiology in rats

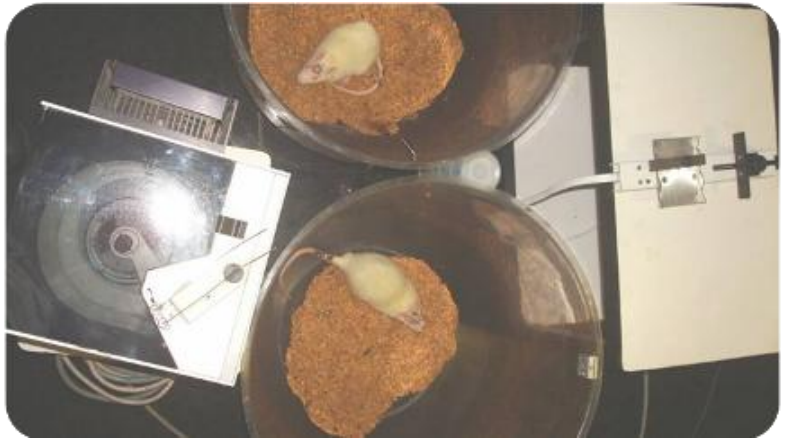


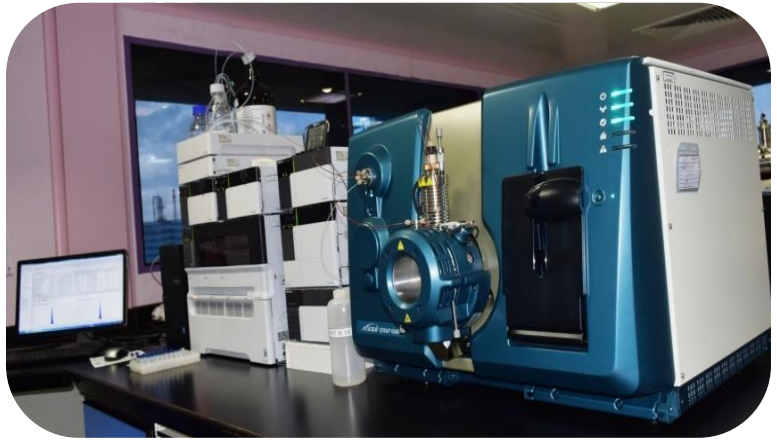




Suven Discovery

State-of-Art Neurochemistry Laboratory





Brain and Spinal Microdialysis

- Neurotransmitter Estimations
- Pharmacokinetics for Target Concentration Assessment
- Species: Rat, Mouse, Guinea Pig

Biomarker Assessments

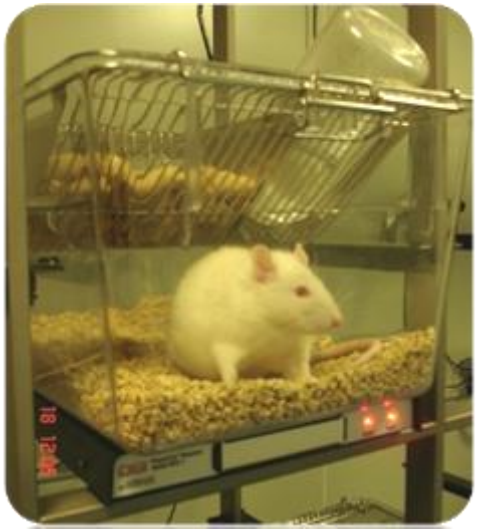
- *In vivo* Profiling for Target Engagement
- Pharmcodynamic Endpoint Assessment
- Species: Rat, Mouse

Animal Models of Neuropsychiatric Diseases

- Chemical/surgical models for AD, PD, Depression
- Behavioral or Neurochemical Endpoint

Suven Discovery

Electroencephalography as a Translational Biomarker



Infrastructure

- Implantable Telemetry System (DSI)
- Acquisition Platform- Ponemah; Data Analysis Software- NeuroScore
- Grass S88 Stimulator
- Species: Rat, Mouse

Evaluations

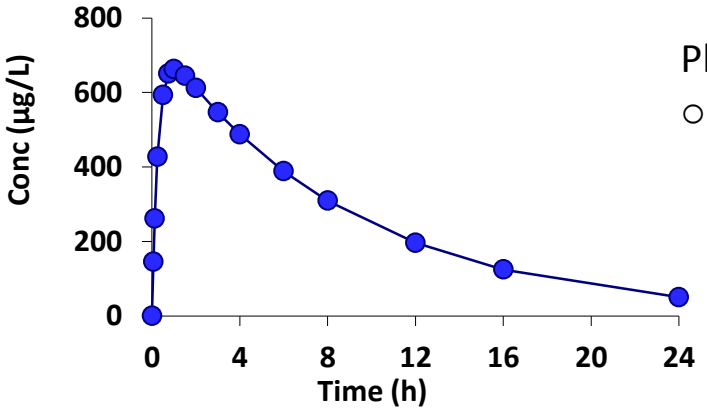
- Sleep/ Wake activity
- Power Analysis in Frequency Bands
- Seizure Detection
- Cognitive Endpoints– Theta and Gamma Modulation
- Orexin-SAP induced chemical lesion model for narcolepsy

EEG Monitoring Combined with Behavioral Assessment

- Open Field for Locomotor Activity
- Object Recognition for Cognition

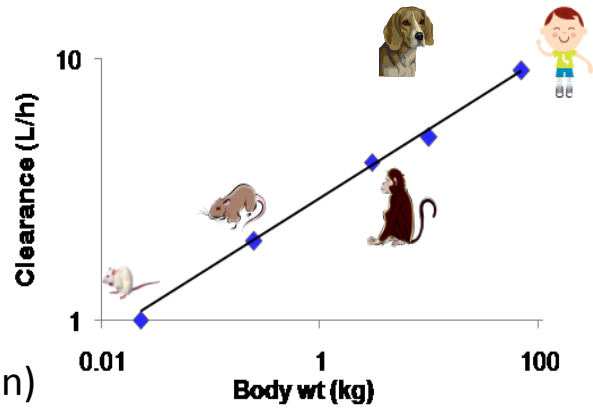
Suven Discovery

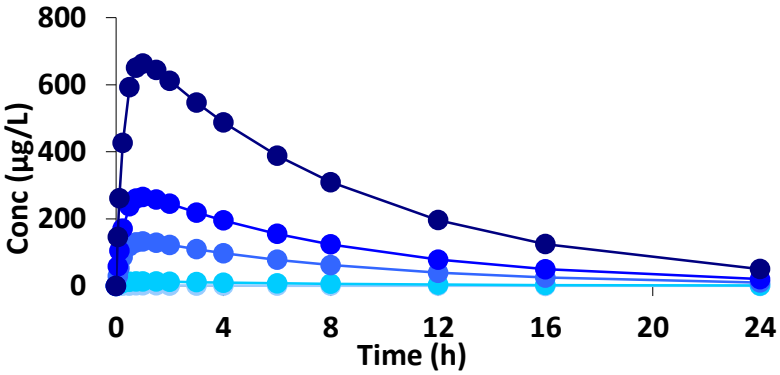
Pharmacokinetic Modeling and Simulation



Pharmacokinetic modeling of animal PK

- Mice to Monkey
  - 1 comp / 2 comp models
  - Determine CL & Vd
  - Allometric scaling
  - Predict human CL & Vd
  - Species difference in metabolism
  - IVIVE (In-vitro In-vivo extrapolation)
  - Microsomes
  - Hepatocytes
  - Consider gut metabolism and permeability in human bioavailability prediction
  - Simulate human PK combining CL, Vd, and Bioavailability
  - Fix PK and Simulate PD





Suven Discovery

Toxicology

The data is generated at extremely rapid pace with the highest quality and scientific integrity to make a go/no-go decision.

4-Day Tox in 14 Days

7-Day Tox in 17 Days

Suven Discovery

Facilities

Animal Facility

- Vivarium spreading over 25000 sft
- Double corridor system
- HEPA filtered 100% clean air supply
- Individually ventilated cages

Pathology Lab

- Well equipped clinical pathology lab
- Necropsy room
- Histology lab
- Spacious archives

Suven Discovery

Toxicology Capabilities

In-vitro cytotoxicity studies

- MTT, LDH and Trypan blue assay
- Phospholipidosis assay

General toxicity studies

- Single dose
- Repeat dose

Genotox studies

- Bacterial Reverse Mutation Test

  (Standard, Mini & Modified)
- *In vitro/ In vivo* Chromosomal Aberration Test
- *In vitro/ In vivo* Micronucleus Test

Clinical Pathology

Anatomic Pathology

Suven Discovery

Rodent Models of CNS Safety

Test	Species	Compound used For Standardization
Irwin's test / Functional Observation Battery (FOB)	Rat or Mouse	MK-801 and Diazepam
Rota Rod	Rat or Mouse	Chlordiazepoxide
Open Field (Locomotor Activity)	Rat or Mouse	MK-801 and Haloperidol
Proconvulsant effect	Rat or Mouse	Pentetrazole
Antagonism of Seizures induced by PTZ	Rat or Mouse	Diazepam
Catalepsy	Rat or Mouse	Haloperidol

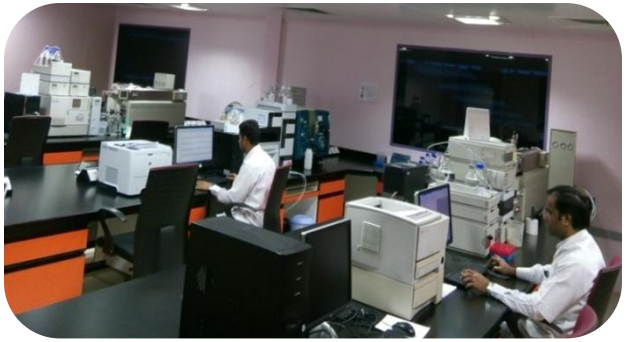
Suven Discovery

Bioanalysis

Facility	State of art bioanalytical labs
Instrumentation	Ultra modern and most sensitive LC-MS/MS instruments (6500QTRAP, 6500QqQ with UHPLCs) LCMS/MS (8), HPLC-UV/FL, HPLC-ECD Deep freezers: -80 °C and -30 °C
Capability	Simple to complex matrices such as tissues and tissue homogenates, CSF, aqueous humor Sample preparation: LLE, SPE, PPT, bead lysis and enzymatic digestion and derivatization
Capacity	Analysis from *in vitro,* clinical and pre-clinical samples (*In vitro*, PK, PD, safety assessment) Simultaneous analysis of parent, metabolite and biomarkers 48 hr turnaround time for study samples (fit for purpose methods) Full validations as per regulatory Metabolite Identification

Suven Discovery

Bioanalysis



Quality System

- Quality Assurance
- ISO/IEC 17025:2005 accreditation

Facility Audits

- US FDA
- Collaborators and global partners

Expertise and Experience

- Can handle most complex design to simple
- Average experience >10 years

Suven Discovery

Preformulation

Screening

- Salt and co-crystal screening
- Crystallization screening
- Polymorph screening

Selection

- Hygroscopicity
- Solubility
- Chemical stability
- Physico Chemical Parameters (Log D, Log P, pKa etc.,)
- Hydrates / Solvates

Solid State

- Thermal properties
- Surface morphology, Particle size
- FTIR, Raman, XRD, Cross Polarized Microscopy, DSC, TGA, DVS etc.,
- Compatibility

Suven Discovery

Pre-clinical, Phase I and II Formulations

- Formulations for Pre-clinical *in vivo* studies
- Solution and Suspensions
- Formulations for Phase I and Phase II studies
- Dosage form Selection and Development
- Immediate Release Tablets
- API-in-Capsules
- Analytical support, Method Validations and Stability studies
- Clinical Supplies Manufacturing and COA generation

Suven Discovery

Novel Formulations

- SEDDS Formulations – Liquid and Solid
- Nano Suspension Formulations
- ODT, ODF and Oral Sprays
- Spray Dried Formulations
- Nano Crystal Formulations
- Liposomes
- Extended Release Formulations
- Timed Release Formulations
- Fixed Dose Combinations

Suven Discovery

Pharmaceutics









Suven Discovery

Quality Assurance

- Independent Quality Assurance team
- Quality System Procedures (QSP's) for Quality System Management and Standard Operating Procedures (SOP's) for Operation, Calibration, Maintenance of Equipment's
- Accredited by ISO/IEC 17025:2005 Quality System since 2005
- Document and Data Control, Conducting Internal Audits, Study Specific Audits
- Dedicated Archive facility for the retention of the records
- Facility audited and approved by many global pharmaceutical companies and majority of Indian Pharma Companies
- Integrity of studies is maintained by following critical components of GLP compliance like SOP, test and control article handling, data handling, training documents, archives etc.

Suven Discovery

Regulatory

- Ensure adherence and compliance with all the applicable cGMP, ICH, GCP, GLP guidelines, regulations and laws
- Preparation of IND documentation in eCTD format
- Experienced in US IND filing
- Acts as a liaison with regulatory agencies and consultants
- Submission of the annual reports for the regulatory agencies
- Qualification of CRO, review and audits

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