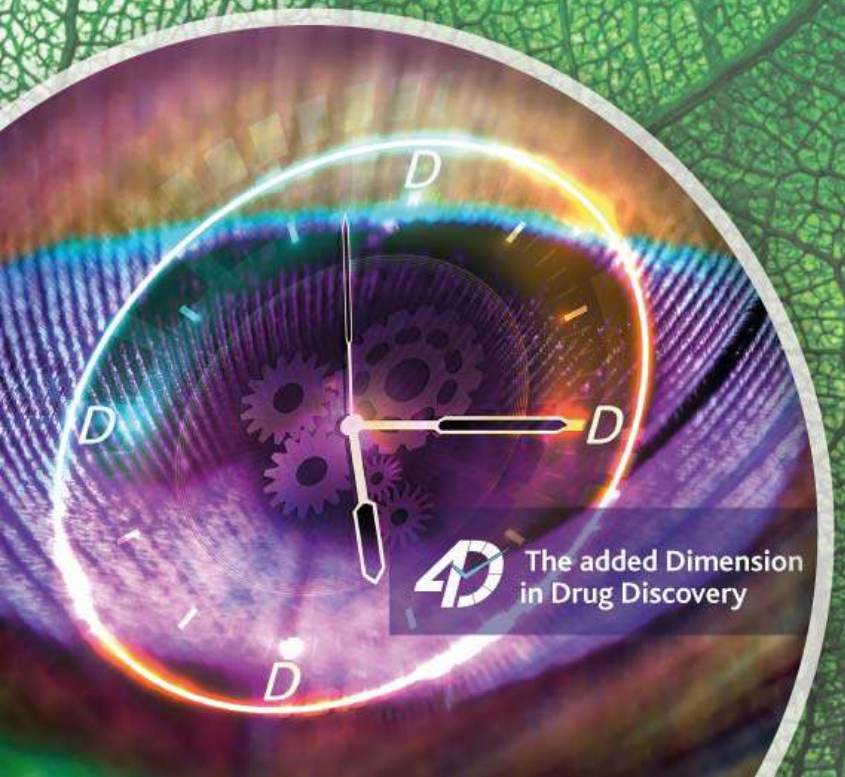
Small Molecule Drug Discovery with the added 4th Dimension- Speed. Introduction and Case-Studies



JUBILANT BIOSYS

Delivering
in
Detail
with
Diligence
and
Dedication

www.jubilantbiosys.com

Moderator– SK Dhakshinamoorthy, VP- Discovery Biology

- Over 20 years of experience in discovery biology & pharmacology
- Accomplished several discovery collaborations with big pharma and biotech companies across United States, Europe & Asia that has led to candidate compounds for clinical development
- Led interdisciplinary drug discovery teams and guided discovery programs spanning multiple therapeutic areas including oncology, metabolic disorders, inflammation, & anti-infectives
- PhD degree in Biotechnology from Anna University, India
- Postdoctoral research at Baylor College of Medicine at Houston, Texas,
- Research fellow at Institute of Molecular & Cell Biology, ASTAR, Singapore- piloted independent research on molecular mechanisms of neuronal cell survival and cell death
- Numerous high impact peer-reviewed publications to his credit

Jubilant Life Sciences – An Integrated Global Life Sciences Company

- A publically listed integrated global pharmaceutical & life sciences company
- Jubilant Life Sciences revenue for FY19 $1,310 million

Life Science Ingredients

- **Specialty Intermediates**
  - Advance Intermediates
  - Fine Ingredients
  - Crop Science Ingredients
- **Nutritional Products**
  - Vitamins
  - Animal Nutrition
- **Life Science Chemicals**
  - Life Science Chemicals
  - Ethanol & Specialty Gases

Pharmaceuticals

Generics

- APIs
- Dosage Formulations
- Indian Branded Pharmaceuticals

Specialty Pharmaceuticals

- CMO-Sterile Injectable
- Radiopharmaceuticals
- Allergy Therapy Products

Drug Discovery and Development Solutions

- Small Molecule Drug Discovery Services
- GMP and Non-GMP NCE Development and supply from full Indian supply chain
- Integrated Discovery Collaborations
- AI/ML efforts enabled with legacy informatics databases

Jubilant Biosys: Innovation Driven Discovery Services Company

Company	Founded in 2000; part of Jubilant Life Sciences
Employees	750+ employees. Most PhDs have >10 years of US/EU experience
Customers	Global top 10, mid-size biotech/ pharmaceutical, and virtual biotech companies
Track Record	Delivered over 75 integrated drug discovery projects

Bengaluru, India

Integrated drug discovery capabilities from target to clinical candidate

Noida, India

Pre-clinical Chemistry capabilities including GMP and Scale-up

Upcoming New Sites
Greater Noida & Bengaluru

Brand new facilities with upgraded infrastructure and capacity

New Facility in Greater Noida

Partnering from Design to Execution Phase

- High safety standards and compliances
- Fully access controlled facility with high security for Data and information
- Designed for high speed and integrated operations with QC, Supply chain, logistics
- Dedicated central analytical areas located on each floor to augment and speed up chemistry delivery

New Capacity Snapshot

Parameter	D-Block Commissioning in 2020 (Phase-1)	B-Block (Phase-2)
Lab space	95,000 sft	40,000 sft
Capacity	350 FTE	135 FTE

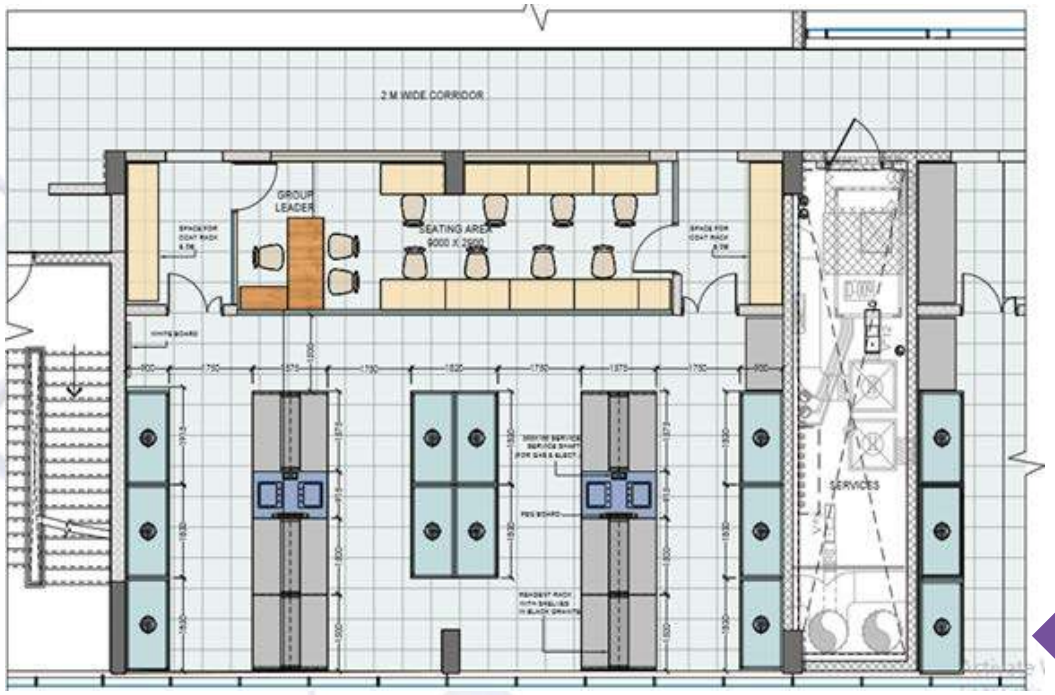
New Site - Current Image
Operations commence in 2020

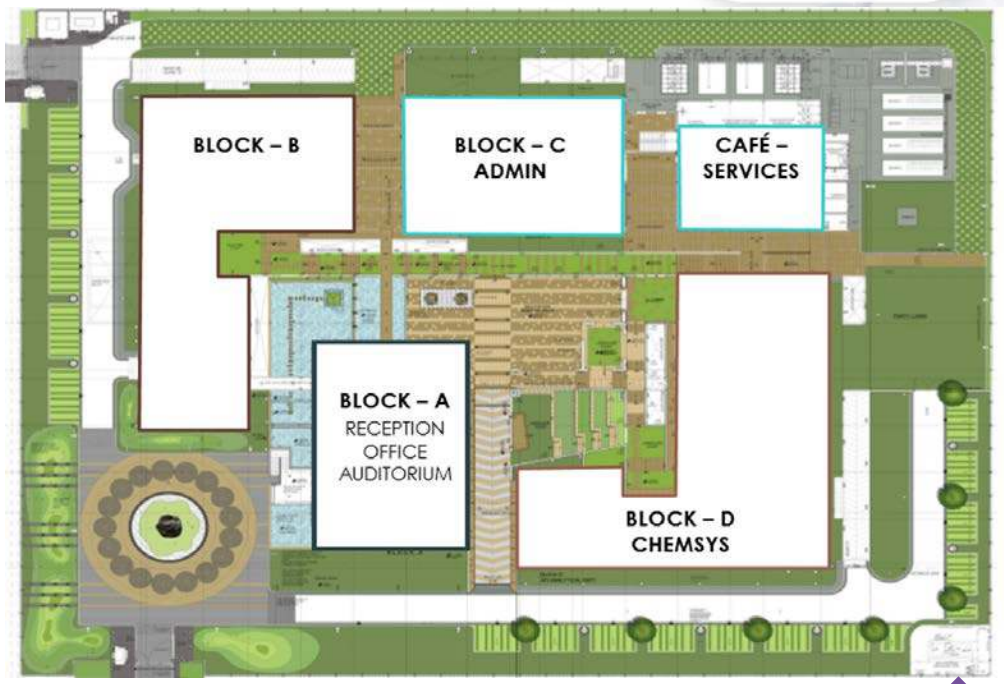
New Site Layout/ Lab Design

Jubilant Biosys Commences Major Capacity Expansions for its Drug Discovery Services Business

CISION PR Newswire

BENGALURU, India, Nov. 28, 2019 /PRNewswire/ -- Jubilant Biosys, a Bengaluru-based subsidiary of Jubilant Lifesciences Limited, today announced commencement of two expansion projects in Greater Noida and Bengaluru.





Layout

Spread-out site with options to expand in gradual manner

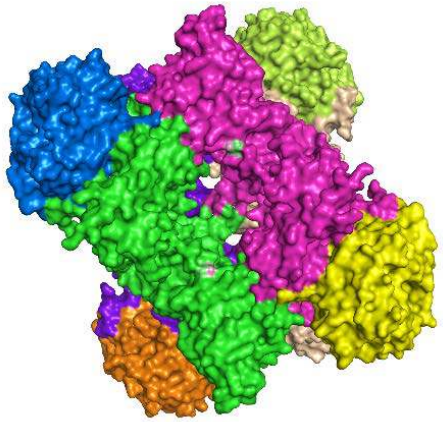
Typical laboratory design

Average size of a 10 fume-hood lab is about 1,500 sft- effectively translates to over 125sft operational space per chemist.

Integration of Drug Discovery Process, Designed for Speed

Target to Lead Generation

- Structural Biology (Protein Science, Crystallography)
- Medicinal, Computational Chemistry
- Informatics/ ML
- Screening & Profiling
- Early ADMET & PK
- *In vitro* & *In vivo* Pharmacology

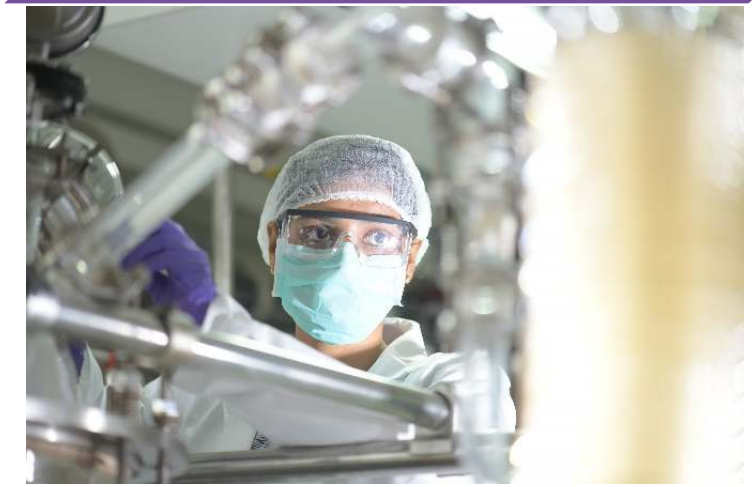


Lead Optimization

- Medicinal Chemistry
- DMPK
- SBDD (Co-crystallization, Computational Modelling)
- Target Engagement & Disease Models
- Safety Profile
- Pre-formulation

Candidate Selection (IND)

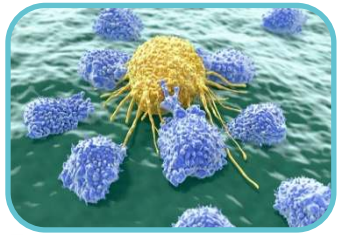
- Process Development
- Scale-up & GMP API Supply
- Genotox
- Non-GLP & GLP Tox
- D2M Predictions (WinNonlin)



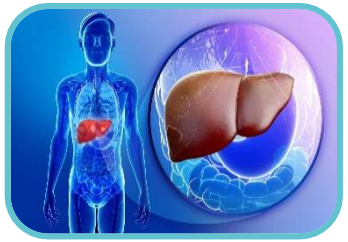
Gained Experience Through a Broad Portfolio of Programs which Drive Successful Outcomes

Disease Biology Expertise

Oncology



Metabolic Disorder



CNS

Pain & Inflammation (P&I)

Kinase

15 + Programs

20 + Programs

GPCR

Enzyme

15 + Programs

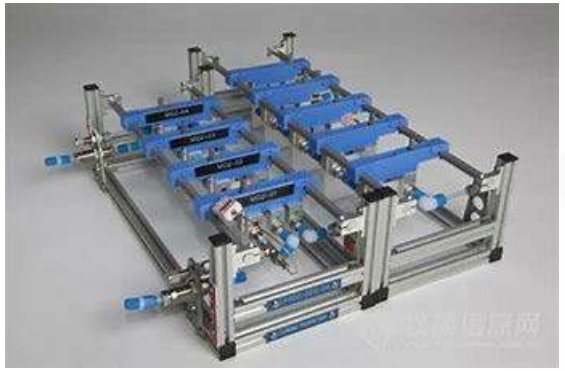
15 + Programs

Non Enzymatic

TV → **Target to Hit** → **Hit to Lead** → **Lead Op** → **Candidate ID** → **Ph I / II**

Emerging Technologies to Foster Speedy Execution

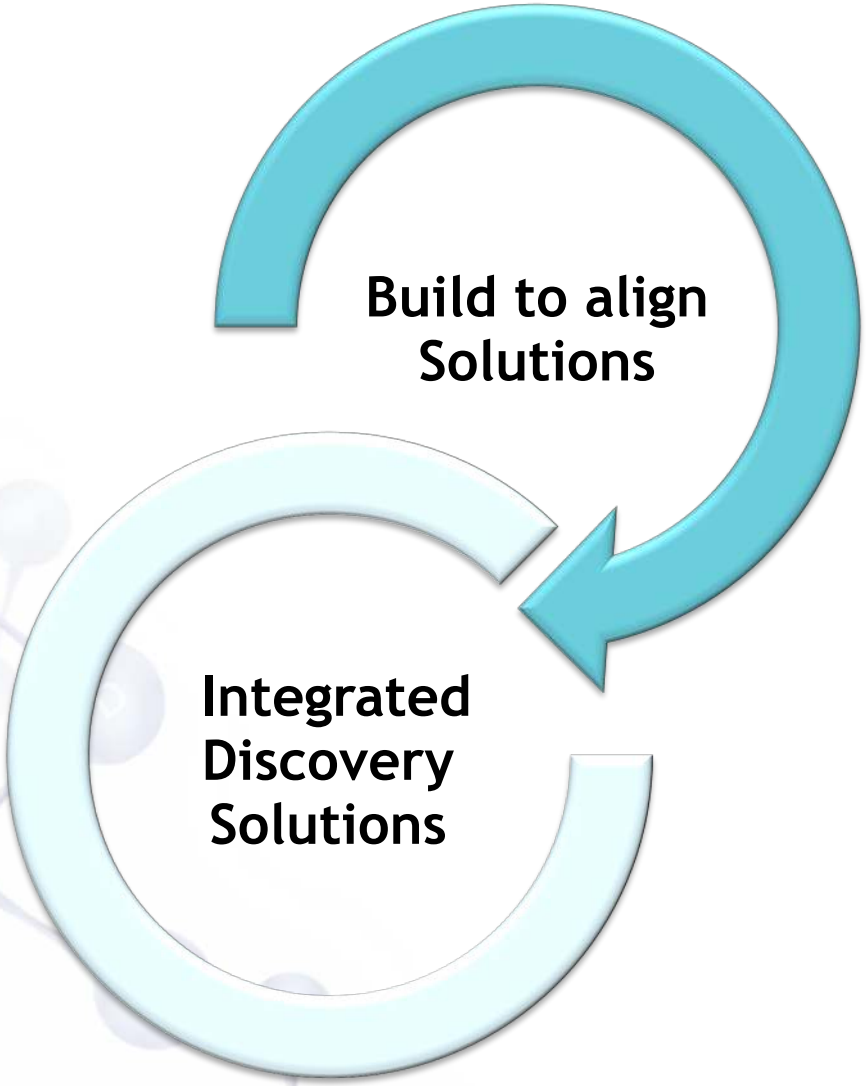
- Flow Chemistry unit, faster, safer and more flexible synthesis with increased speed and improved quality
- SPR, label free real time detection of molecular interactions
- RapidFire, LCMS/ MS based high-throughput screening system
- AI/ML Platform, in depth data analysis, drug repurposing
- Digital adoption; edocroom, eLAN (CDD Vault) to enabled 24x7 information access



RapidFire 365 – new plate handling

…accelerating decision making for our clients' programs

Biosys Flexible Business Models made for Speed, Sustainable Innovation & Outcomes to Our Clients



Discovery, Preclinical & Clinical Solutions (FTE / FFS)

Medicinal & Synthetic Chemistry, Structural Biology, Molecular Modeling, Discovery Biology, Pharmacology, Bioinformatics, Bio analysis, Toxicology, Scale-up, cGMP

Risk Share Model for Integrated Drug Discovery Programs

Across therapeutic areas- Oncology, CNS , MD and P&I

Target to Candidate Selection

Testimonials

"Jubilant functions as a fully integrated part of our project team. One of the things that really distinguishes them as a partner for us is they are extremely good at communicating "

-Michael Gallatin,
President & Co-founder
Mavupharma

Our primary CRO, the one which has really been central to the success of our company, is Jubilant Biosys. They are headquartered and have major facilities in India, plus the U.S. and Europe.

In terms of technical capabilities, Jubilant are extremely competent in medicinal chemistry, in drug metabolism, toxicology, structural biology, biology, all the aspects that one needs for the projects and work we do at Mavupharma.

They are both our intellectual and strategic partners. It's not a case of "Here's your contract, CRO, now go run your tox study and send us the report when you're done."

Jubilant functions as a fully integrated part of our project team. One of the things that really distinguishes them as a partner for us is they are extremely good at communicating. Sounds basic, but it isn't, and it's absolutely critical to the success of our wo at Mavu.

Now & Next

"Jubilant brings a real sense of camaraderie- almost a selflessness- to do what's best for every project"

-Siegfried Reich,
Co-founder & SVP
eFFECTOR Therapeutics

I was just describing the value of "team" in the field of drug discovery, and at eFFECTOR. Jubilant is an integral part of our team and of so much of what we've done and have accomplished to date. It's a true team effort.

Every one of our projects—all the way from the inception to the very large-scale synthesis, which Jubilant is helping us with tremendously. They're doing all the large-scale stuff for us right now up to kilogram quantities material, and have done so for our more advanced programs They just continue to do phenomenal work for us, and they're highly effective and highly efficient as well.

I interact with a lot of people out in the larger industry, and I've worked with lots of different CROs. There are some good ones out there. But Jubilant has been special for us. The level of daily interaction, feedback and trust that have been established between our organizations is just phenomenal. They're also really great people, too, kind and easy to work with, which really helps. It's all about the relationship that we've been able to build and forge with them.

Biosys: Information Security Given Top Priority Through Detailed Measures

IT Infrastructure

- Jubilant Proprietary Softwares used:
- Chemical Tracking System (CTS)
- Compound Management System (CMS)
- eAnalytics – for paperless access to compound analytics by project team
- eDocRoom - Secured document Sharing Portal for data sharing with external clients
- Chemdraw as Structure Editor.
- ELN from CDD Vault for Cloud based customer access

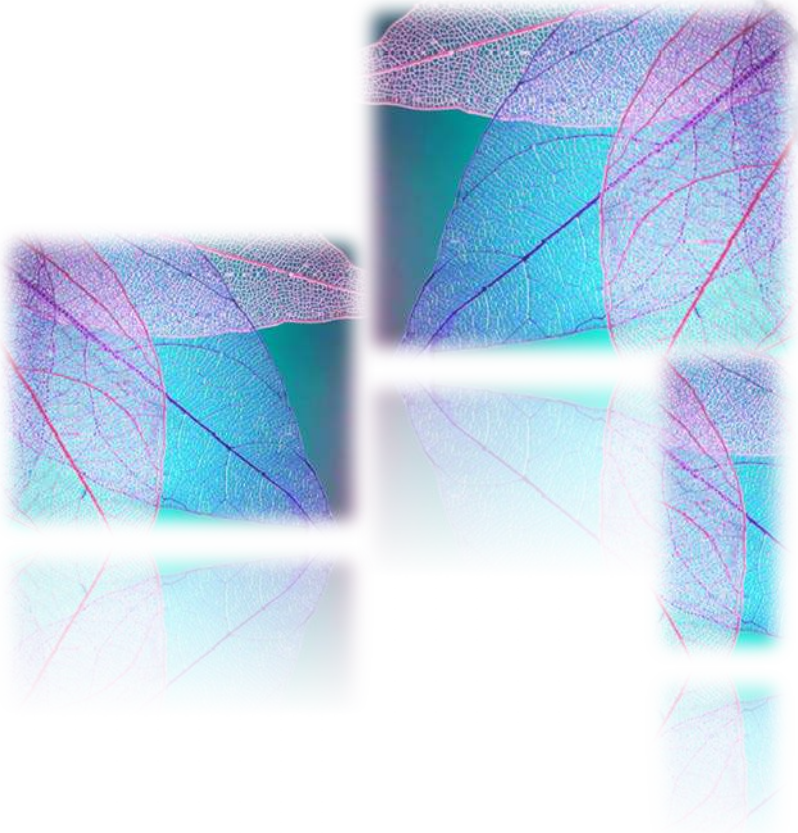
Data Integrity & Confidentiality

- Websense Data Leakage Protection (DLP)
- Seclore for classifying Data PGP Encryption
- IBM360 solution for Mobile Device Management
- Appropriate Policy & Procedure defined for Backup & Restoration
- Restoration Drills
- Offsite back-up data storage

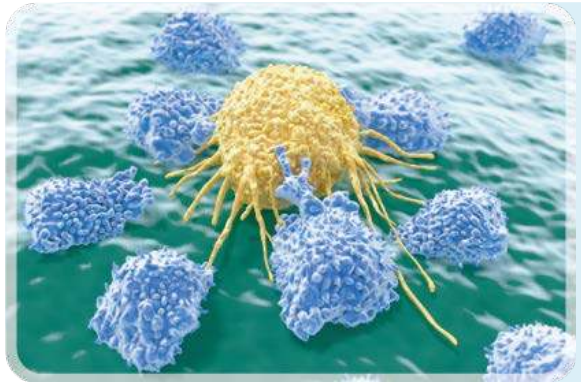
Data Security

- Symantec Backup Exec solution
- RAID enabled servers to host applications & file server
- Approved Offsite Disaster Recovery Plan (DRP)
- Hardware Redundancy available at Network, Firewall, Proxy, Mail server that guard against downtime
- Internal Compliance management Tool
- Mobile Applications, Chatbot, Summit Tool
- Emails on Microsoft Cloud – O365

Overview of Disease Biology & Functional Expertise



Oncology: Deep Experience Resulting in 17 Milestones



- 25 Programs
- Disease pathways /mechanisms
  - RTKs, PI3K/AKT, MAPK, enzyme and others
  - Epigenetics, Kinases, Immuno-Oncology and GPCRs
  - Specific tumor types, prostate, NSCLC, hematological and others

In-Vitro Assays

- **Cell Free Biochemical:** TR-FRET, AlphaLISA, ADP-glow others
- **Target Modulation:** Autophos, ELISA, alpha-screen, MSD, Western Blot, flow cytometry, PCR
- **Cell Cycle:** FACS analysis; Cell migration
- **Matrix Invasion:** Matrigel and HUVEC
- **Proliferation & Apoptosis:** Alamar blue, Annexin V, caspase activation
- **Immune Modulation:** Immune-profiling, T cell proliferation and co-culture
- **Others:** FLIPR, ICC, 3-D culture, assay for epigenetic target

In-Vivo Models

Xenograft (Subcutaneous) Models for PK-PD or Efficacy

- Lung (NCI-H82, HCC827, Calu-6)
- Ovarian (A2780)
- Prostate (PC3, DU-145)
- Gastric (MKN-45)
- Hematological cancers (MV-4-11, Pfeiffer, CCRF-CEM, MM1.S)
- Breast (MDA-MB-231)
- Colon (HT-29, Colo-205, HCT116; LoVo)
- Pancreatic (PANC-1; Bx-PC3)
- Melanoma (A375)
- Other tumors (A431, U-87 MG)

- **Orthotopic** (Breast, Prostate, SCOT, Glioblastoma)
- **Syngeneic** (B16-F10, CT26 and 4T1)
- **Matrigel Plug Angiogenesis**

Metabolic Disorders: Expertise in First-in-class Targets with Novel Mechanisms of Action

- 16 Programs
- Milestones achieved - 11
- GPCR's, Kinases, Enzymes and Ion channels

In-Vitro Assays

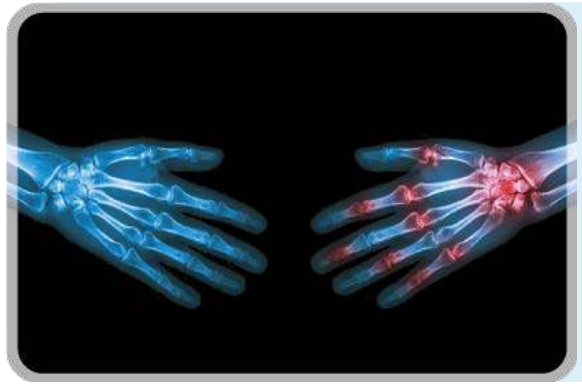
- **Assays:** Insulin secretion, glucose uptake, glucagon secretion, incretin release [GLP-1, CCK, PYY, GIP] beta cell protection; Adipogenesis, adipolysis; Apo B secretion, fatty acid oxidation; membrane potential; Transporter; assessment of Gene/ Protein modulation
- **Cells:** Islet, Hepatocytes, Muscle
- **Cell Lines:** 3T3L1; C2C12; L6
- **Platforms:** High Content Imaging; MSD; ELISA; RapidFire LCMS/MS; SimpleWes; Western Blot; Immunocytochemistry

In-Vivo Models

- Streptozotocin-Type 1 diabetic; STZ-induced diabetic neuropathy; STZ induced Diabetic Nephropathy
- **DIO:** body weight, glucose, insulin, lipids, and pair-fed studies
- **Genetic:** ZDF, ob/ob, db/db
- **Incretin and endocrine secretion:** [GLP-1] in mice
- **Acute and Chronic:** OGTT, IPGTT (Glucose & Insulin) in mice and rat
- **Acute:** malonyl CoA lowering in rats
- **Lean diabetic:** (STZ + Nicotinamide)
- **NASH:** choline-deficient, L-amino acid-defined, high-fat diet

Recent Publication: A small molecule inhibitor of NicotinamideN-methyltransferasefor the treatment of metabolic disorders; **SciRep.2018 Feb 26;8(1):3660;**

Pain and Inflammation (P&I): Focus on Immuno-inflammation



- 13 Programs
- Milestones achieved - 8
- Ion channels, GPCR's, Kinases and Enzymes
- Collaborated with top pharmaceuticals and biotechs to target various pain pathologies

In-Vitro Assays

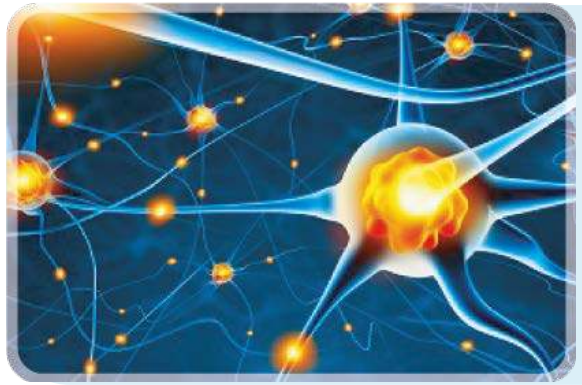
- T-cell proliferation; T- cell migration; immune (multiplexing, MSD platform); IKK and NF-κb reporter; JAK-STAT pathway; Kinase [PI3K, AKT, P38; MAPK, JNK]; Chemotaxis
- Rat macrophage culture and multiple cytokine measurement using MSD technology
- In vitro microglia and astrocyte culture from rodent brain and functional
- CGRP release from spinal neurons, Neurite outgrowth, neuroprotection and toxicity
- Protein translation, Multiple unfolding protein response (UPR) assays

In-Vivo Models

- Neuropathic Pain models: CCI induced neuropathic pain in mice and rats , L5/L6 ligation(SNL), SNI in mouse, Paclitaxel induced pain (cancer), Bone cancer pain, STZ induced Diabetic Neuropathy;
- Inflammatory Pain models: Formalin, CFA, Carrageenan
- Inflammatory Bowel Disease: DSS, TNBS and oxazalone-induced colitis in mice (acute and chronic)
- Arthritis: Collagen induced arthritis
- Respiratory and Atopic Allergy Models: Steroid sensitive and resistant asthma in mice; LPS-induced neutrophilia in rats
- Fibrosis Models: Lung, liver, skin, kidney, NAFLD and NASH
- Others: Psoriasis, EAE (MS model), Uveitis in rabbits, rats & mice(ocular models)
- PK-PD correlation

Recent Publication: Synthetic analogues of the parasitic worm product ES-62 reduce disease development in in vivo models of lung fibrosis; Acta Trop. 2018 Sep;185:212-218;

CNS: Deep Expertise -Neuro-Degeneration, Psychiatry, Neuro-Inflammation



- Collaborated with big pharma, biotechs and with start-ups
- Worked in a spectrum of target class including Ion Channels, Kinases, Enzymes, Transcription Factors

In-Vitro Assays

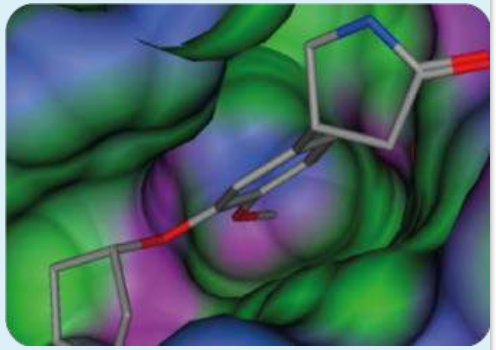
- In vitro microglia and astrocyte culture from rodent brain and functional (measurement of IL1b, IL6 and TNFa)
- Phospho-tau and Amyloid beta measurement using MSD or ELISA
- CGRP release from spinal neurons
- Neurite outgrowth, neuro-protection and toxicity
- Protein translation
- Multiple unfolding protein response (UPR)
- Numerous cellular assays using iPSC neurons from AD patients

In-Vivo Models

- **Neuro-Degeneration:** Amyloid beta isoform, total and phospho-tau, UPR signaling, stroke models
- **AD Mouse Model:** access to transgenic mice APP, tau and others from Taconic
- **Cognition:** Novel Object Recognition Task [NORT]
- **Psychiatry:** Forced swim test
- **Neuro-Inflammation:** MOG induced MS
- **Target Engagement:** Several ex-vivo binding target modulation
- PK-PD correlation

Chemistry - Discovery & Development Capabilities

Medicinal Chemistry



Over 75 integrated programs across TA's

Hit / Lead identification

Lead optimization

SAR development

Chem-informatics, Computational chemistry and Structural biology

Target landscape analysis

Synthetic Chemistry

Scaffolds, Building blocks, Intermediates, Reference compounds

Library design and synthesis

Asymmetric synthesis (Stereoselective, enzymatic and resolution techniques)

Impurity / Metabolite synthesis

10 mg to 100 g

Process Research/GMP

Process design, development and optimization

Process safety studies

Tech Transfer cGMP and Non - GMP material supplies for Tox, Pre-clinical, Phase 1 / 2

IND filing support

100g to 10 kg

Analytical Research

GLP Method development and validation

Purifications (including chiral compounds)

Stability studies (ICH)

Physical characterizations (DSC, TGA, XRD)

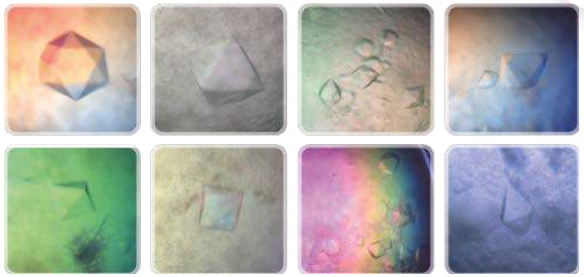
Impurity profiling

Reference standard characterization

Structural Biology- Proven expertise in Protein Structure Determination

Highlights:

- Multi construct approach for structural studies
- E. coli, Insect cell (Baculovirus) & Mammalian expression systems
- Co-expression, limited proteolysis, deglycosylation skills
- In-house X-Ray facility & access to Synchrotron (Australia)
- Supported multiple discovery programs by co-crystal structure determination



Build to align Solutions

Expertise

- Assay grade
- Biophysical grade
- Crystallization grade

> 300 proteins

> 100 targets (different target classes)

Culture capacity

- E. coli - 60-80 L/ week
- Baculovirus– 24 L/ week
- Mammalian– 4-6 L/ week

Integrated Discovery Solutions

~10 Novel structures

~ 250 co-crystal structures

~ 50 targets

Target classes :

Kinases, Phosphatases, Proteases, Deaminases, Lyases, Isomerases, Carboxylases, Dehydrogenases, PDEs, Epigenetic targets, Chaperone, Apoptosis protein, Interleukins & receptors, and Oncogenic transcription factors

Cell Line engineering

Cell lines

- CHO
- HEK293
- HEK293S

Stable cells and Characterization

- * Plasmid mediated expression
- * Viral mediated expression
- Functional characterization

Recent Publication: Crystal structures of monkey and mouse NNMT bound with end product, 1-methyl nicotinamide. BBRC. 2017 Sep 16;491(2):416-422.A small molecule inhibitor of Nicotinamide N-methyltransferase for the treatment of metabolic disorders; Sci Rep. 2018 Feb 26;8(1):3660

DMPK – Rapid, Reliable and High Quality Data

Absorption

Permeability

- Caco-2 (A –› B and B –› A)
- PAMPA; MDCK-MDR-1

Solubility

- Aqueous (various pH)
- SGF and SIF

Pharmacokinetics

- Mice, Rats, Rabbits, Guinea pigs, Hamsters
- Dogs (outsourced)
- Cassette dosing
- Micro-sampling in mice
- Dose escalation studies
- DBS (dried blood spot)

Distribution

Protein binding

- Equilibrium dialysis (ED) method to determine fu in plasma, tumor & brain
- Ultra filtration

Tissue distribution

- In Rats (using cold compound)

Cross functional

- PK-PD
- Toxicokinetics
- D2M prediction
- Preclinical formulation

Metabolism

Metabolic stability

- Liver microsomes
- S-9 fractions and Hepatocytes

CYP

- Inhibition & induction

Metabolite ID

- In vitro using liver microsomes, hepatocytes
- In vivo from plasma, bile, urine and feces
- Glutathione trapping
- Blood/plasma partitioning
- Time dependent inhibition
- Plasma and Chemical stability

Excretion

Mass balance
(metabolic cages)

Biliary and Urinary excretion

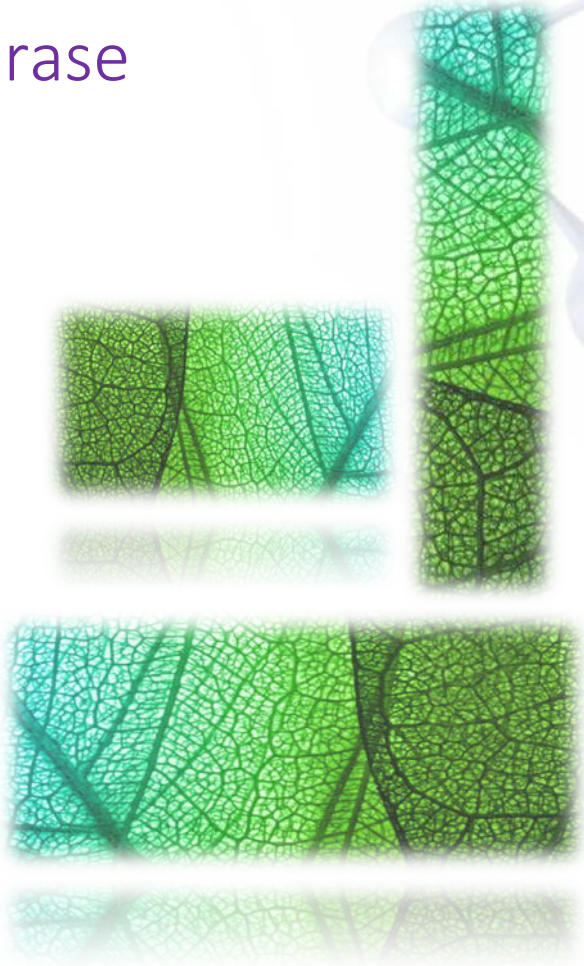
Turnaround time

- 5-6 Days most of the in vitro studies
- 6-7 Days for IV and oral PK study

Toxicology: Rapid, Reliable and High Quality

General (GLP/Non-GLP)	Genetic (GLP/Non-GLP)	Histology	Clinical Pathology
• Maximum Tolerable Dose (MTD) study • Single dose toxicity study • Dose range finding study • Repeated dose toxicity study (4, 7, 14 and 28 day) • Toxicokinetic studies	• Ames study / Mini-Ames study • Micronucleus test (In vivo & In vitro) • Chromosomal aberration test (In vivo & In vitro)	• Animal Necropsy and Tissue Grossing • H & E Staining • Special Staining • Microscopic Evaluation	• Hematology • Clinical Chemistry • Urinalysis • Coagulation • Cytopathology • Bone Marrow Evaluation

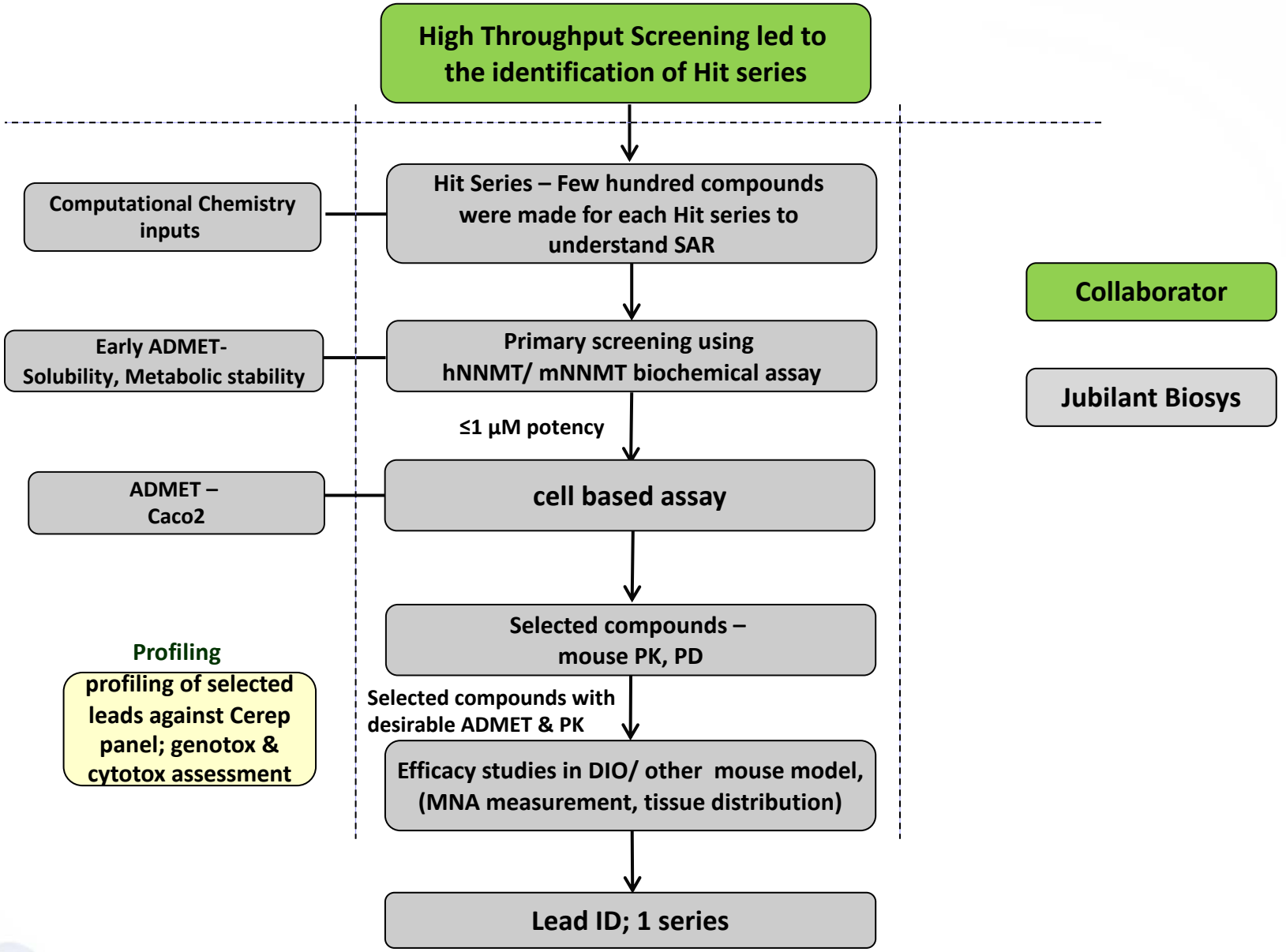
Case Study 1: Inhibitors of Nicotinamide N-methyltransferase for the treatment of metabolic disorders – An integrated drug discovery collaboration with a Big Pharma



Target - Nicotinamide N-methyltransferase (NNMT)

- NNMT is a cytosolic enzyme that catalyzes the transfer of a methyl group from the co-factor S-adenosyl-L-methionine (SAM) onto the substrate, nicotinamide (NA) to form 1-methyl-nicotinamide (MNA).
- Higher NNMT expression and MNA concentrations have been associated with obesity and type-2 diabetes.
- NNMT is predominantly expressed in the liver and in adipose tissue.
- NNMT is implicated in various disease conditions including metabolic disorders.
- NNMT expression and activity are high in white adipose tissue (WAT) samples of mouse models of obesity and insulin resistance (ob/ob, db/db and diet-induced obese (DIO) models).
- Higher NNMT expression was detected in isolated adipocytes from obese as compared to non-obese humans.
- Population studies indicate that MNA levels strongly correlate with obesity and diabetes.

Flow Chart

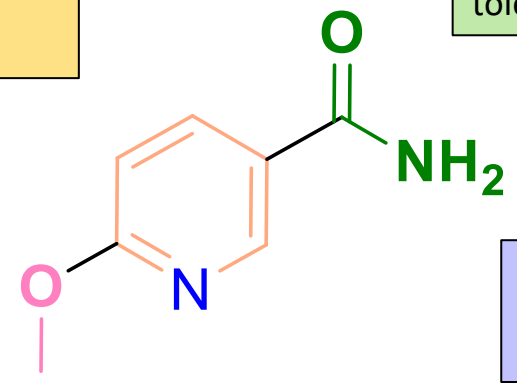

High Throughput Screening led to the identification of Hit series
Computational Chemistry inputs
Hit Series – Few hundred compounds were made for each Hit series to understand SAR
Early ADMET- Solubility, Metabolic stability
Primary screening using hNNMT/ mNNMT biochemical assay
≤1 µM potency
ADMET – Caco2
cell based assay
Selected compounds – mouse PK, PD
Profiling
profiling of selected leads against Cerep panel; genotox & cytotox assessment
Selected compounds with desirable ADMET & PK
Efficacy studies in DIO/ other mouse model, (MNA measurement, tissue distribution)
Lead ID; 1 series
Collaborator
Jubilant Biosys

SAR - Nicotinamide Derivatives

Small fluoro substitutions are not tolerated, replacing pyridine with pyrimidine leads to loss in potency

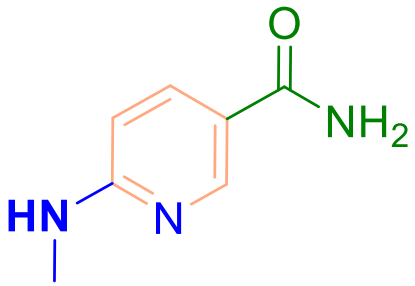
Bioisosteres of amide lead to loss in potency, extension of NH with arylalkyl group is not tolerated

Replacing OMe retained potency



JBSNF-00088
h/mNNMT= 2.4 uM

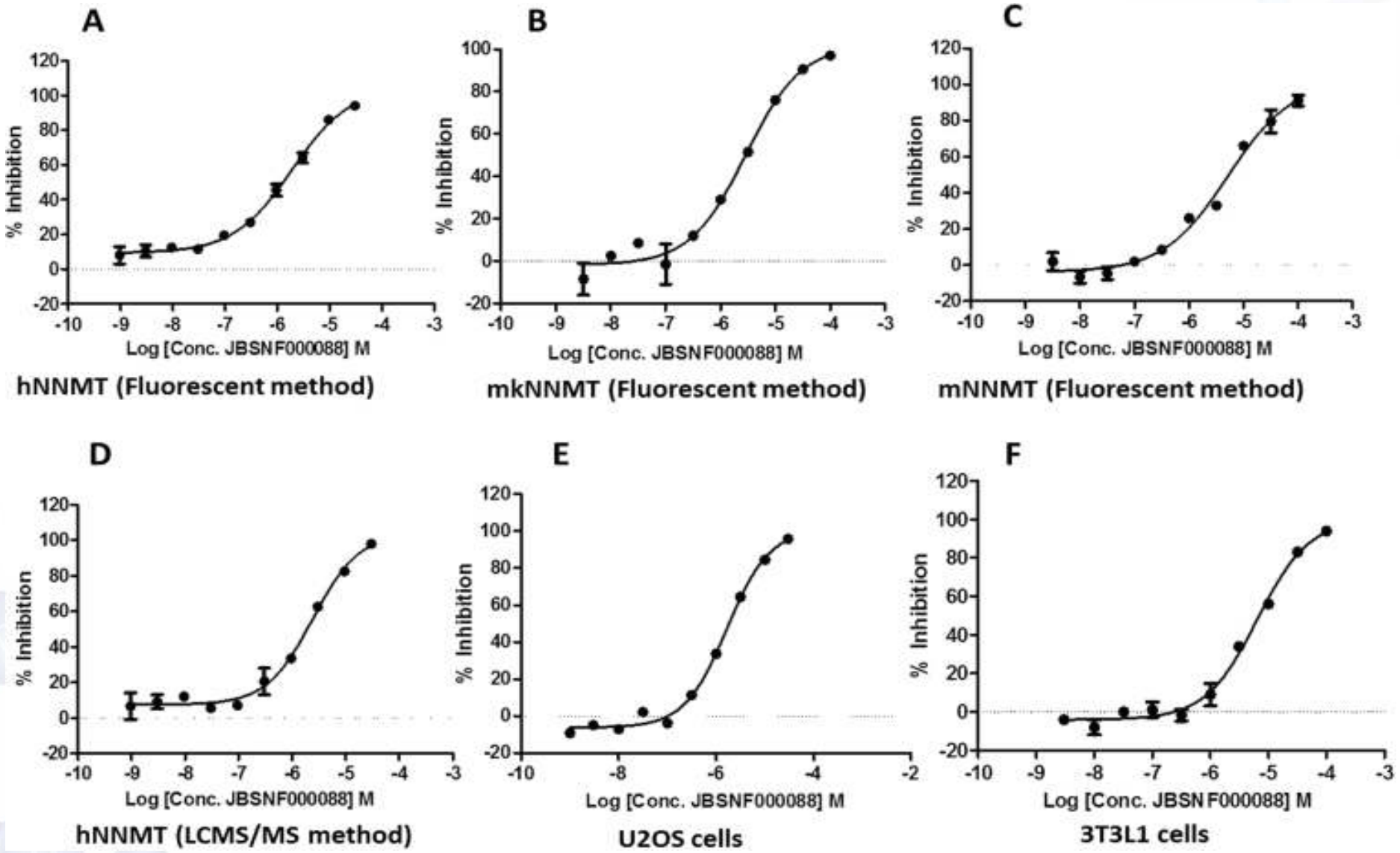
Nitrogen is essential for the activity



JBSNF-00265
h/mNNMT=0.59 uM

Disubstituted amines are not tolerated
Replacing Me with cyclopropyl/pyrrolidine is not tolerated

Profile of Compound JBSNF-000088 in Enzymatic and Cell Based Assays



JBSNF-000088 inhibits human, mouse and monkey NNMT enzymatic activities in biochemical assay (A,B,C). Inhibition of human NNMT enzyme was demonstrated using LCMS/MS based enzymatic assay (D). Cell based assays were carried out using U2OS cells (E) and differentiated 3T3L1 cells (F).

ADME, PK and Safety Profile of JBSNF-000088

Parameter	JBSNF-000088
Metabolic stability h/r/m microsomes (% remaining)	90/91/79
Solubility (µM)	208
Caco-2 permeability (nm/sec)	252
Caco2 Efflux ratio	1.04
Cyp Inhibition	>20µM
Cl/Vd/F%-mL/min/kg and L/Kg	20.5/0.69/43
Ames test	Negative
Micronucleus test	Negative
Selectivity panel	clean[a]

[a]BSNF-000088 was tested against a panel of 34 receptors, transporters and enzymes.

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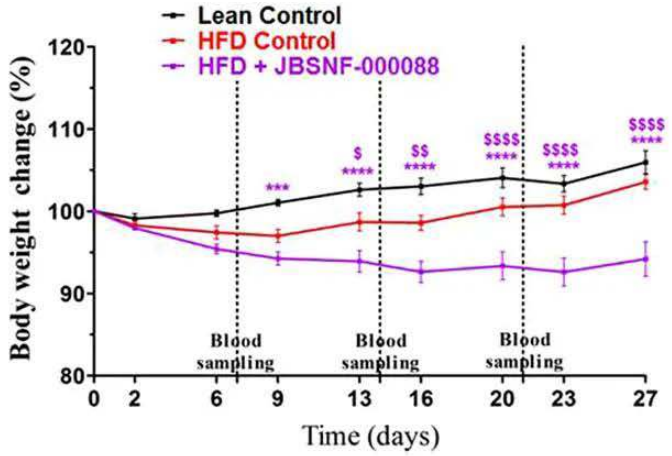
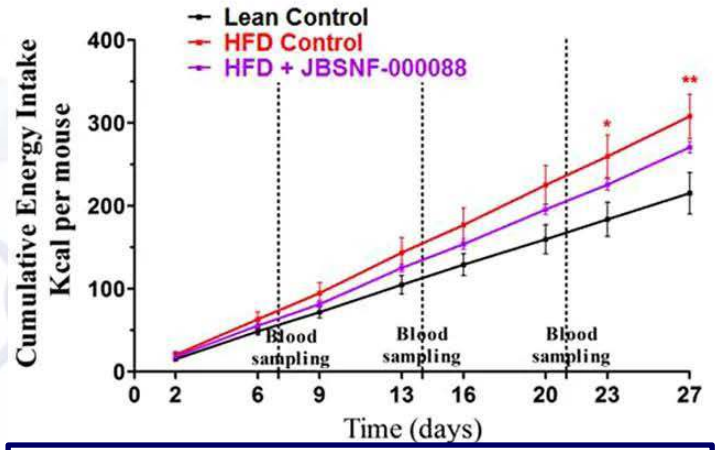
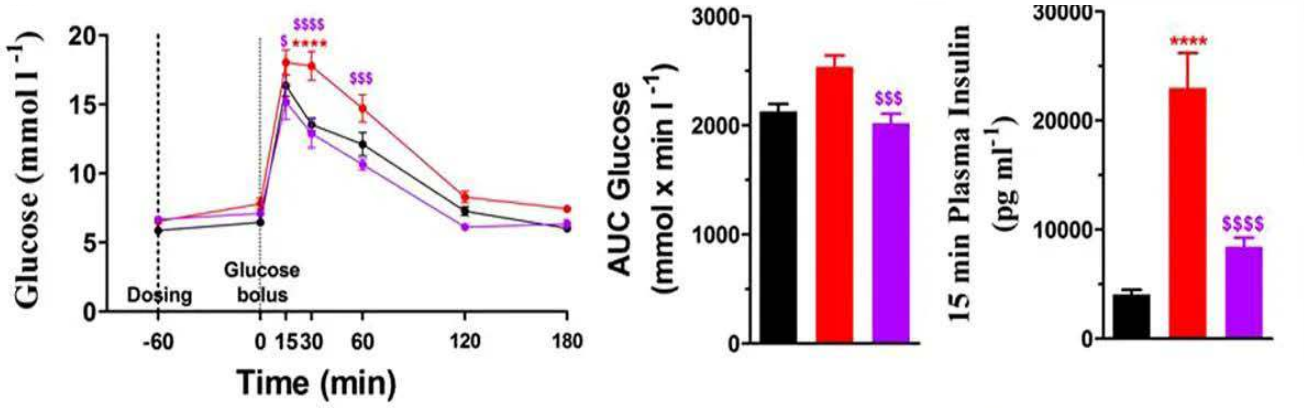
Effect of 4-w Treatment with JBSNF-000088 (50 mg kg−1 bid) in Mice with Diet-Induced Obesity

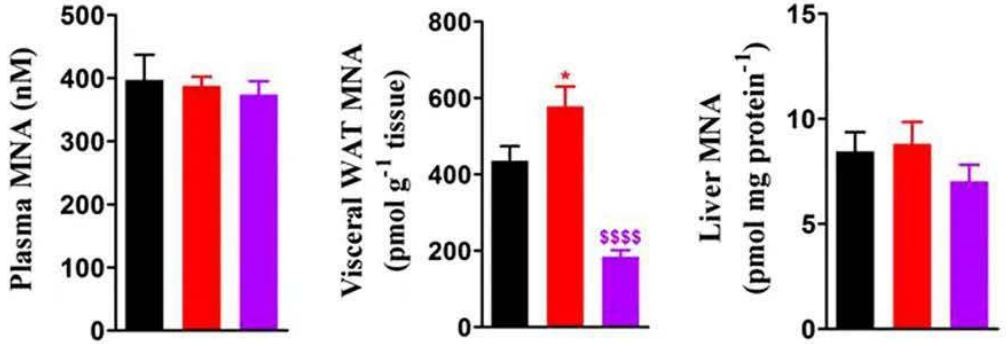




Body weight changes (%) and cumulative energy intake in lean control animals and HFD fed animals treated with vehicle or JBSNF-000088.



OGTT profile, AUC of blood glucose, 15 min plasma insulin, 0 min plasma insulin, 0 min blood glucose and HOMA-IR index in lean control animals and HFD fed animals treated with vehicle or JBSNF-000088.



MNA concentrations in plasma, visceral WAT and liver samples of lean control animals and HFD fed animals treated with vehicle or JBSNF-000088.

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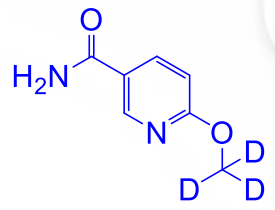
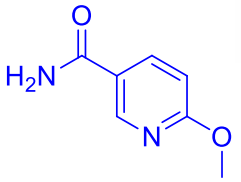
Profile of Key Compounds-Nicotinamide Series

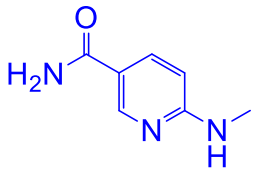
	JBSNF-000088	JBSNF-00265	JBSNF-000292
M.wt/clogP/tPSA	152/0.6/64	151/0.3/67.5	155/0.6/64.7
h NNMT enzymatic assay IC_{50}µM	2.5	0.58	2.1
Metabolic stability h/r/m/hum-hep (% remaining)	90/91/79/71	85/97/69/56	84/83/85/70
Solubility (µM)	208	~200	211
Caco2 Efflux ratio	1.04	1.2	0.9
Cyp Inhibition (3A4, 2D6, 2C9, 2C19)	>20 uM	>20 uM	>20uM
Cmax PO/IV (10/1 mpk)	3568/1051	1433/587	4523/661
AUC PO/IV (ng.h/mL)	3508/786	1087/511	5776/957
$t_{1/2}$ PO/IV (h)	0.52/0.41	1.2/0.8	1.1/0.9
Cl/Vd/F% mL/min/kg and L/Kg	20.5/0.69/43	27.9/1.85/19	16.6/1.25/58
MNA reduction invivo 50mpk P.O.	~40% reduction for 2hr	80% reduction for 2hr	70% reduction for 4hr
Cerep panel-44/Ames	ND	clean	clean



JBSNF-000292



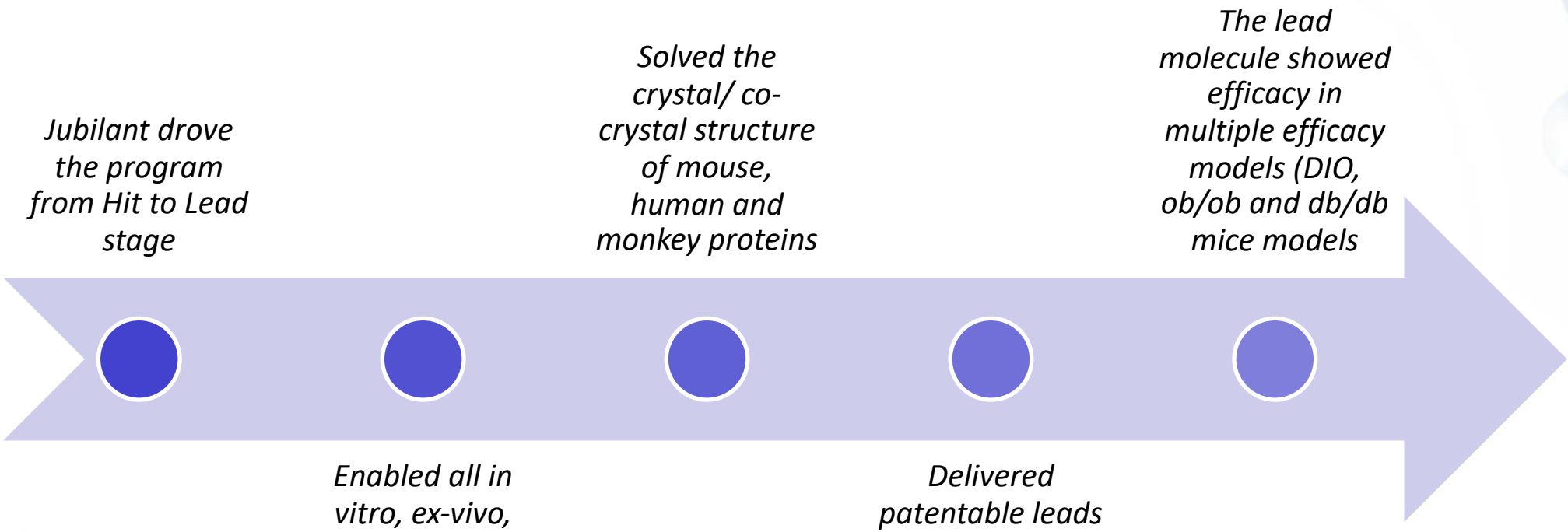
JBSNF-00088



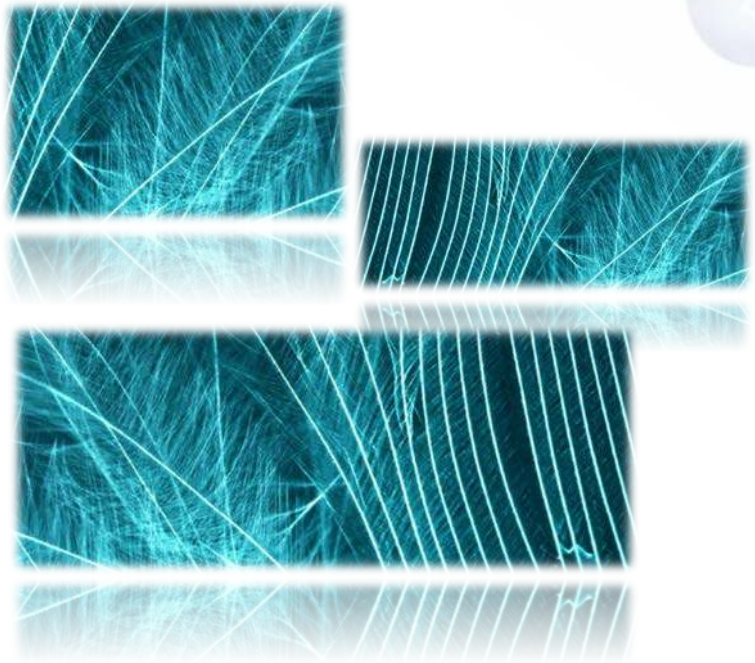
JBSNF-000265

First case of a small molecule NNMT inhibitor showing pharmacological benefits in vivo

Key Accomplishments in the Program



Case Study 2: Small molecule inhibitors of a target known to modulate STING pathway– An integrated drug discovery collaboration with a Biotech in US

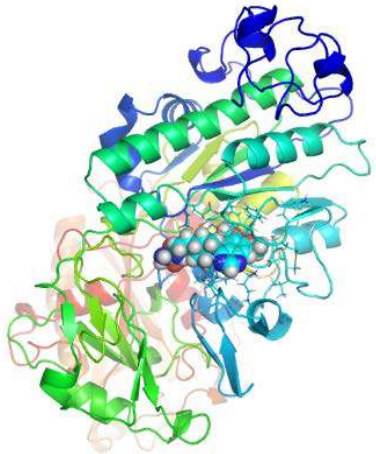


Target for Immuno-Oncology

- Target: Immuno-oncology
- Indication: Cancer
- Collaborator: Virtual US Biotech
- Project Goal: Target to PCC
- Type: First-in-class
- Starting Points: No Hits, started from virtual screen
- **Goal: Designing and development of selective, safe, and orally available small molecule inhibitors of a target known to modulate STING pathway**

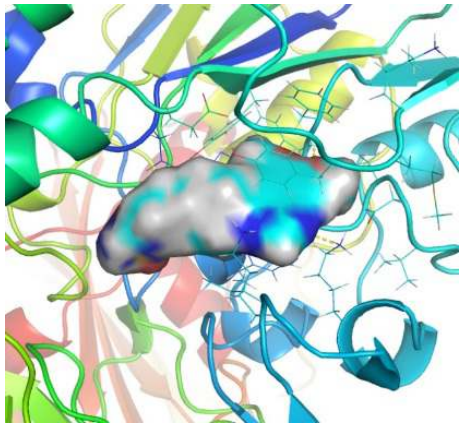
First-in-Class Mechanism, Preclinical Candidate

Objective	To discover orally available small molecules to address unmet medical needs in oncology
Deliverables	Delivered a pre-clinical development candidate and couple of back up series for oncology in 18 months



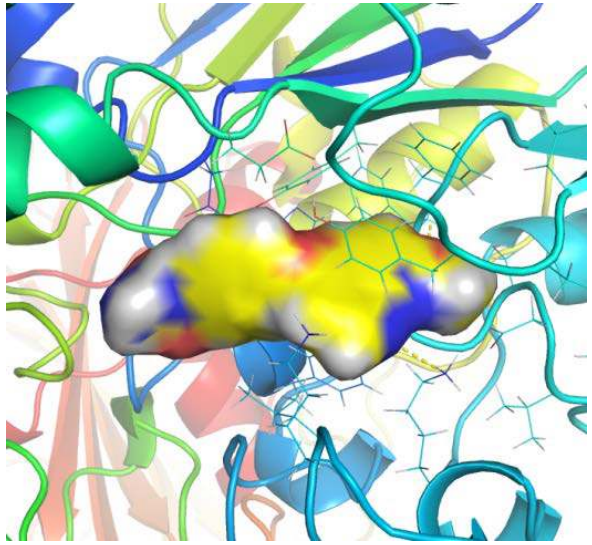
Homology model/
Virtual screening

+



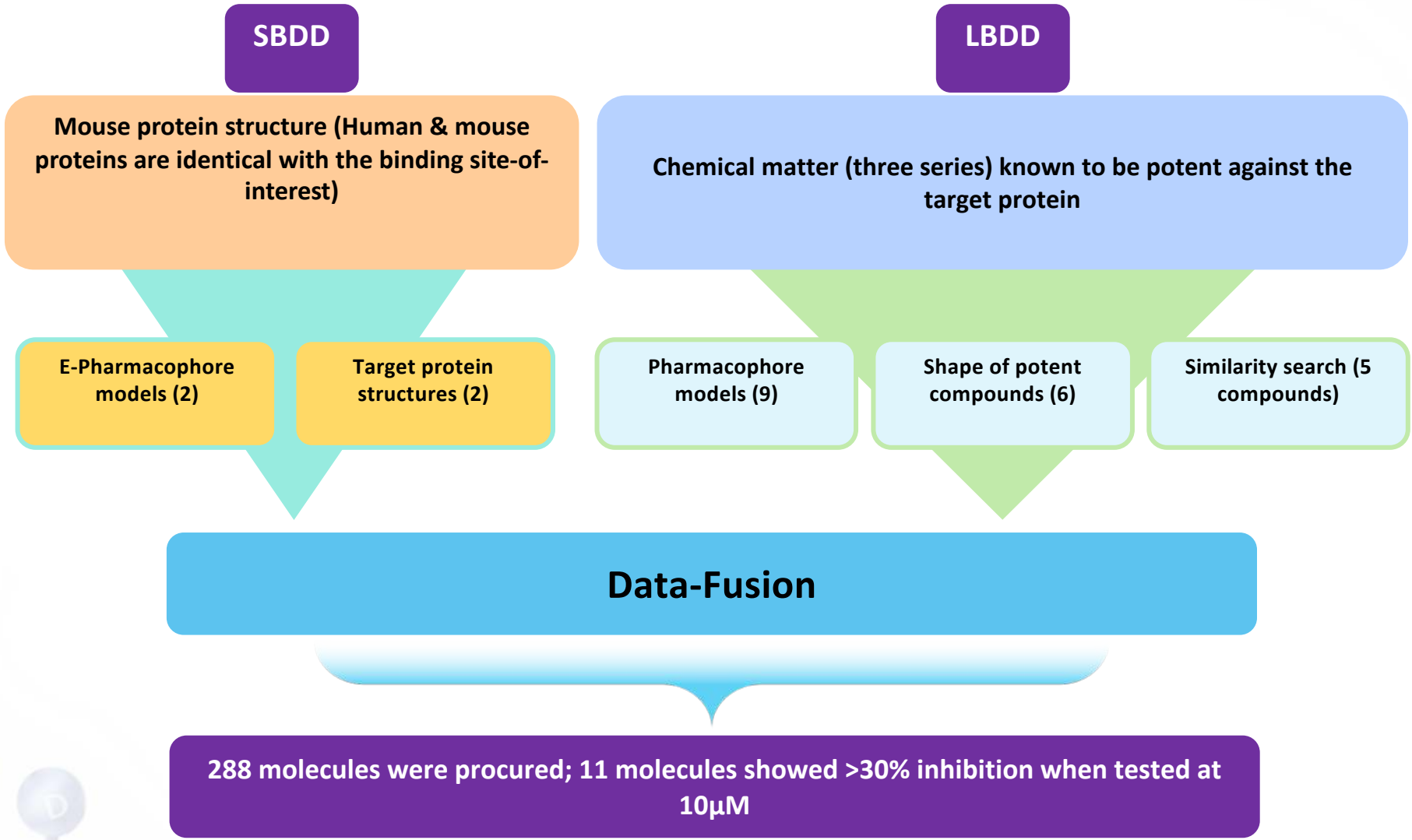
Structural biological
analysis

synthesis and
evaluation



Rational Design

Virtual Screening to Derive the early Hit Series

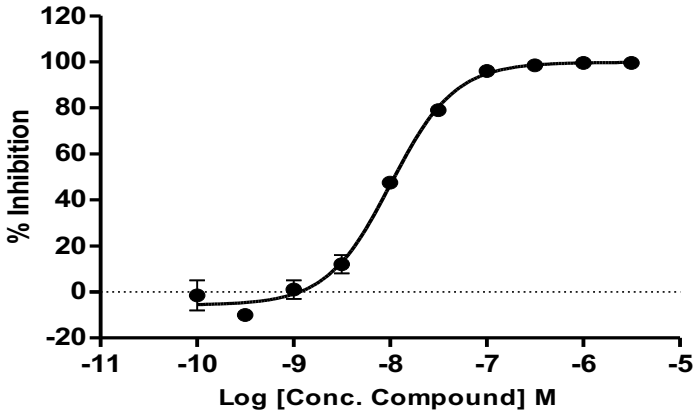


Chemical Evaluation Towards Developmental Candidate

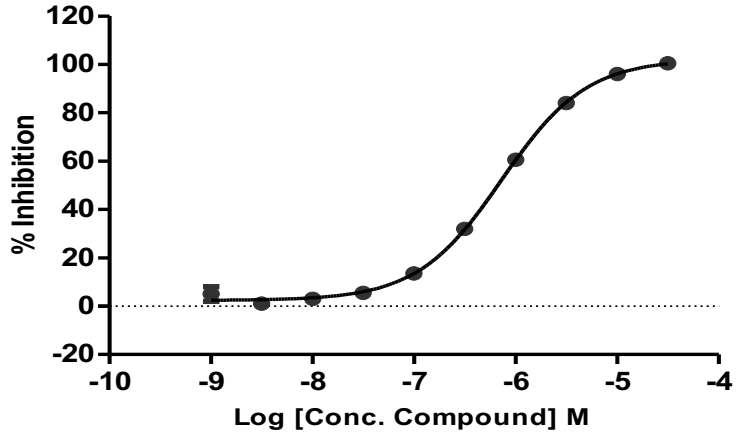
PARAMETER	DDC TARGET VALUE	Compound-1	Compound-2	Compound-3	Compound-4
Enzyme (Ki, nM)	< 10 nM	✔	✔	✔	✔
Solubility	> 10 µM	✔	✔	✔	✔
Permeability (Caco2 A→B)	> 1 E6/cm-s	✔	✔	✔	✔
Efflux Ratio (Caco2)	< 10	✔	✔	✔	✔
Human microsome met	< 50% in 30 min.	✔	✔	✔	✔
CYP inhib. (3A4, 2C9, 2D6)	IC_{50} > 10 µM	✔	✔	✔	✔
Rat Clearance (mL/min/kg)	< 70% HBF	✔	✔	✔	✔
Rat PK: terminal half life	≧ 2 hr	✔	✔	✔	✔
Rat PK: oral bioavailability	≧ 30%	✔	✔	✔	✔
Dog PK	>30% F, CL ≤ rodent	✔	High Cl	✔	✔
Human Hepatocytes	no unique major hu met.	✔	✔	✔	✔
Selectivity; LeadProfile screen	Activity > 10 µM	✔	✔	✔	✔
hERG Patch clamp	>30x margin at predicted efficacious C_{max} (fu)	IC_{50} = 3.6 µM	✔	✔	✔
Selectivity vs kinases	Not promiscuous inhibitor	Moderately active for Aurora Kinase B	✔	✔	✔
Non-GLP Safety Data	Favorable profile	Low safety margin	Low safety margin	Low safety margin, renal toxicity observed	✔

Biochemical Assays Drove the SAR

- Profiling carried out using Luminescence and Calorimetric based Biochemical assays
  - Luminescence assay



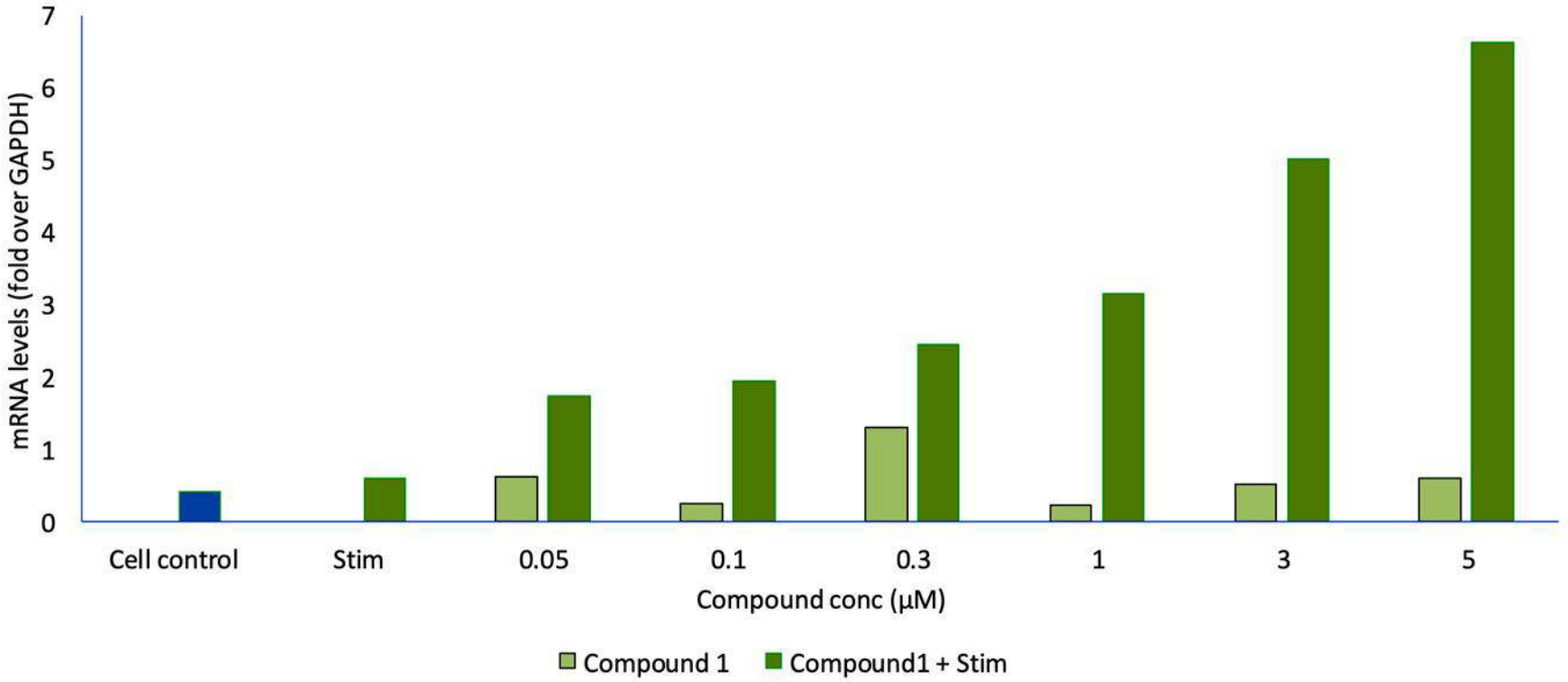
  - Colorimetric assay



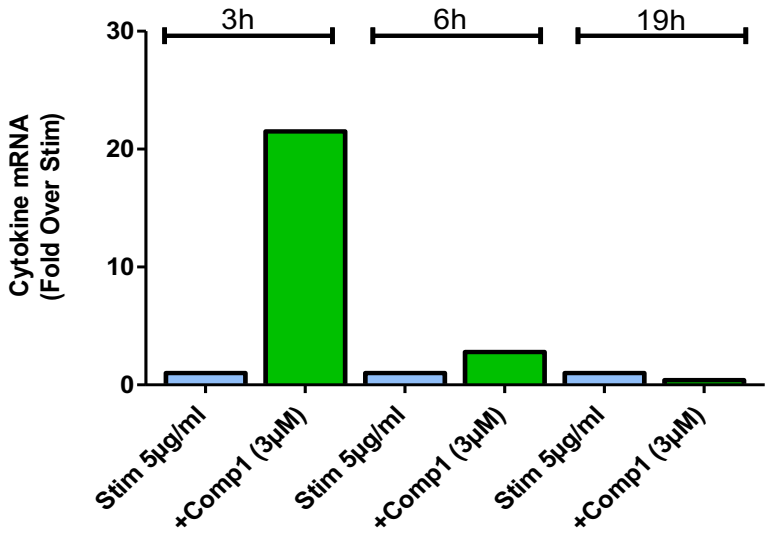
Secondary Cell-Based Assays to study Downstream Effector Modulation

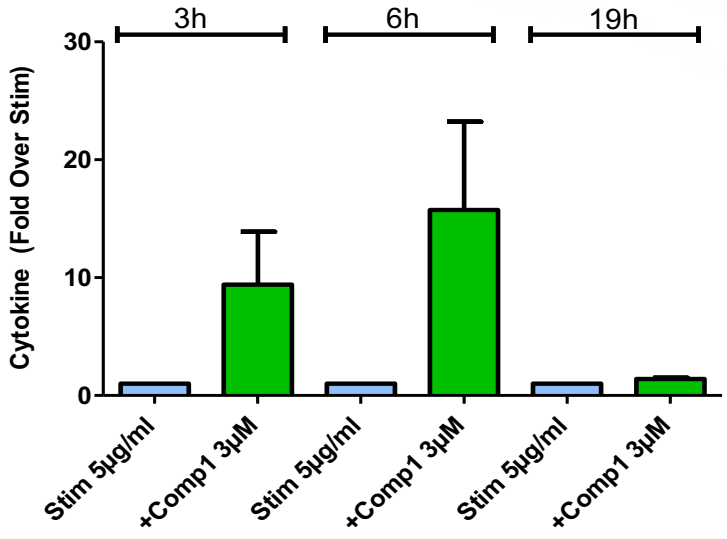
Assays using human fibroblasts:

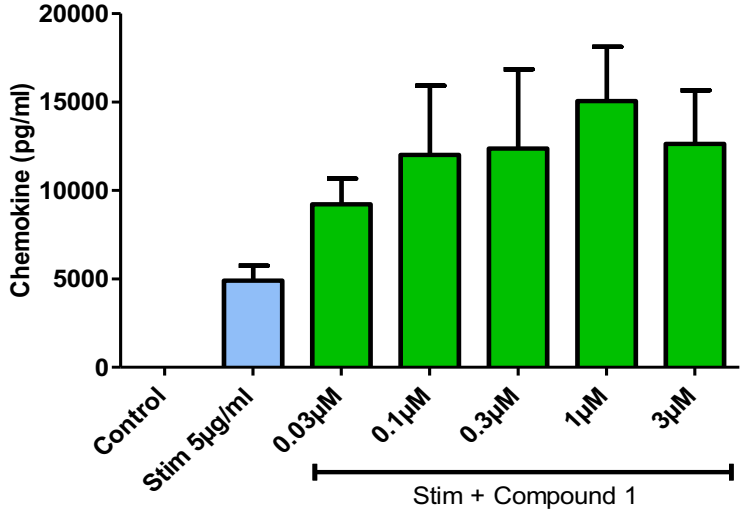
- Cytokine mRNA measurement



Proof-of-Concept studies using PBMCs

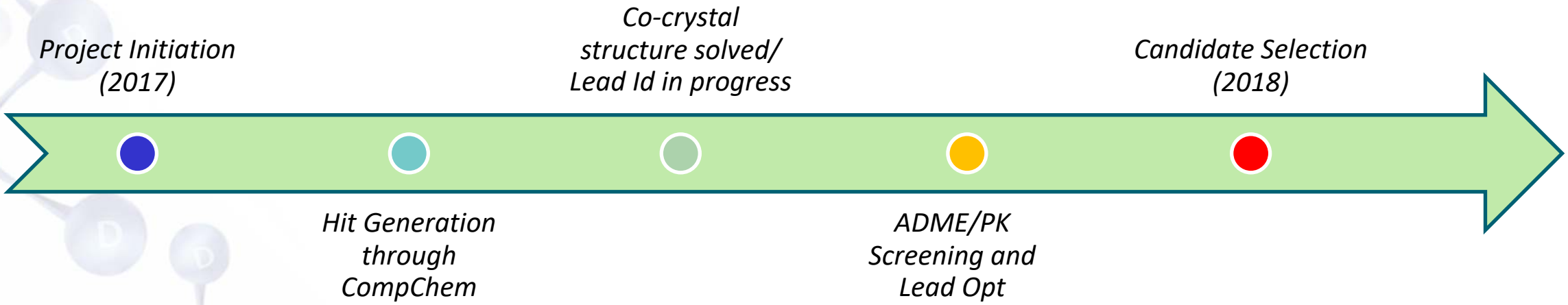






Key Accomplishments in the Program

- Jubilant spearheaded the program as the collaborator was a virtual biotech
- Enabled all in vitro, ex-vivo and functional assays
- Solved the crystal/ co-crystal structure
- Delivered multiple scaffolds which are patentable
- A novel pre development candidate was delivered in less than 18 months
- The candidate showed efficacy in multiple tumor models
- IND enabling studies are in progress and expected IND filing in 2019/2020



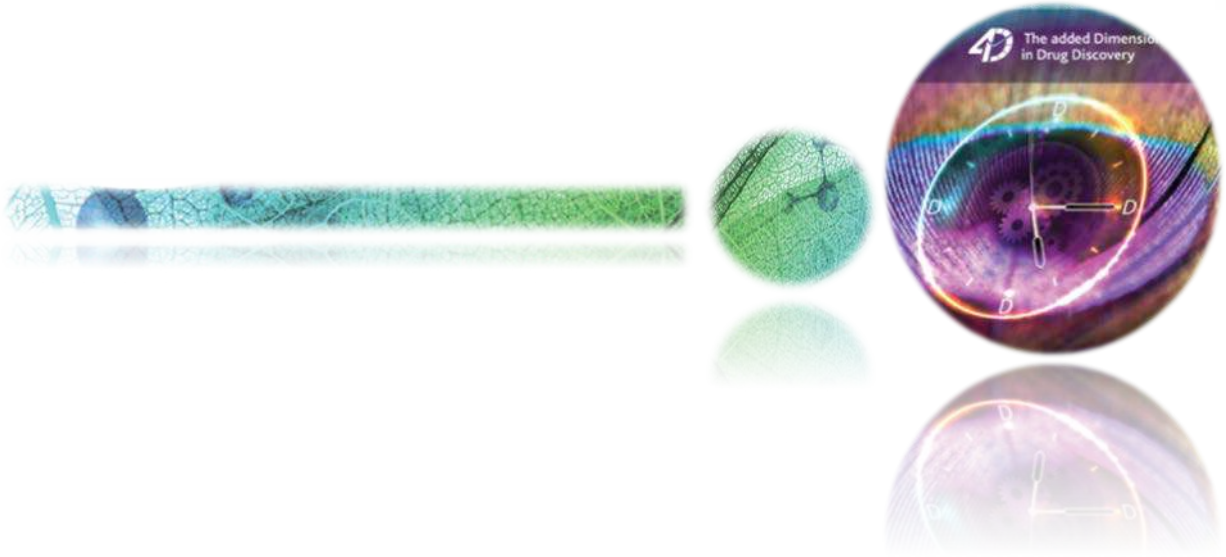
Why Jubilant Biosys?

"We share your passion of Drug Discovery & Development"

- A highly experienced scientific team; delivered >75 integrated discovery programs
- New technologies applied to accelerate drug discovery and improve decision-making quality
- A boutique CRO with a talented team of >550 scientists giving your program priority
- Investing in the future of drug discovery and development through expansion
- Leadership with global pedigree in US, EU and Japan

Questions & Answers

“We are keen to understand your challenges”



Thank you for your time

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