



**AURIGENE**  
Accelerating Discovery



# Aurigene: Specialized Services

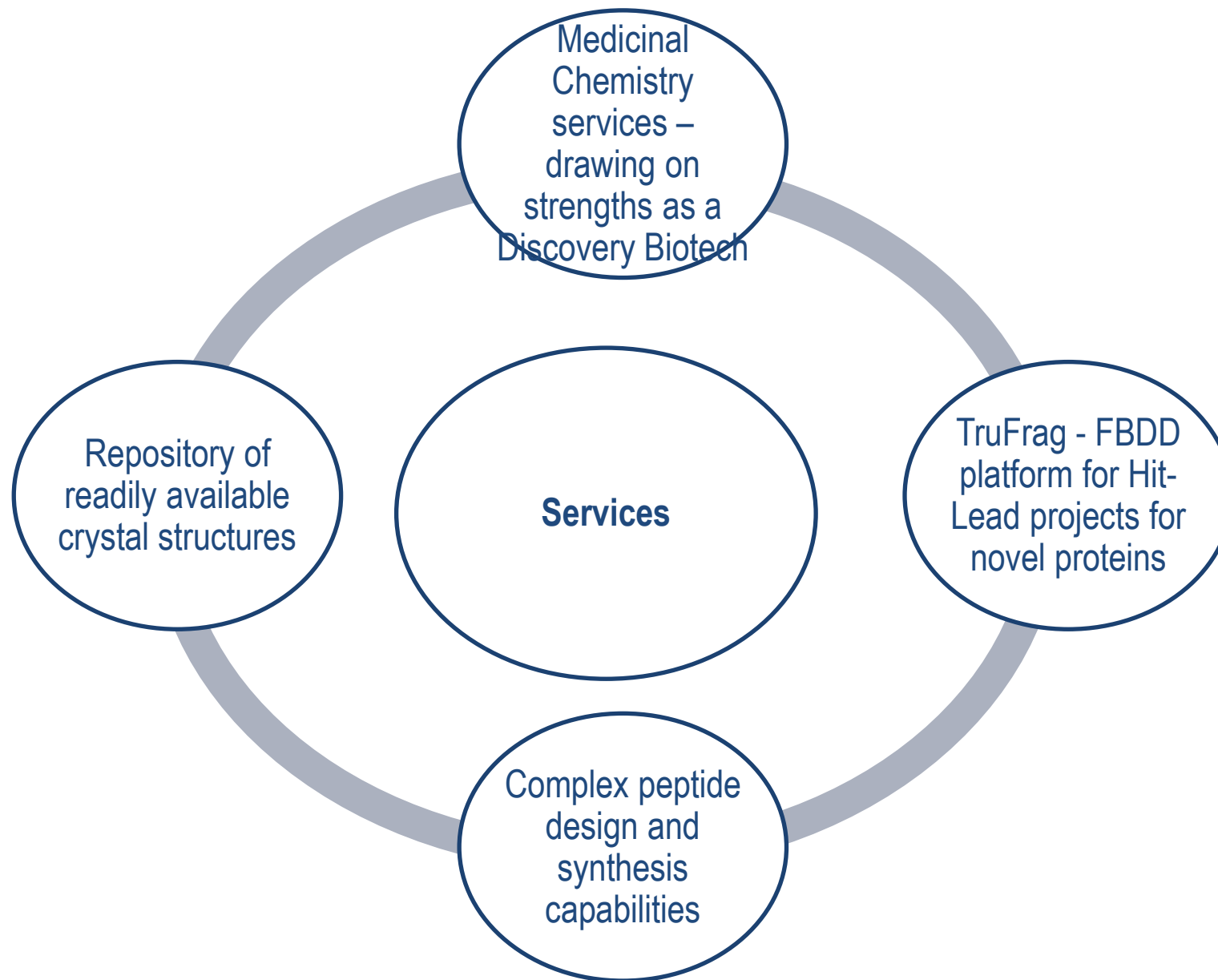


# Aurigene: Introduction



- Aurigene is a specialized biotech focused on
  - oncology and
  - inflammatory disorders
- Fully integrated drug discovery engine, over 575 scientists
- Pioneering a “collaborative drug discovery” model: built on leveraging strengths
- Experience
  - in over 35 targets/ programs
  - with 6 of the top 10 pharma companies and
  - 5 other partners worldwide
- Licensed multiple early-stage programs; strong pipeline of differentiated programs
- Core technology strengths in Structural Biology
- Small molecule and peptide expertise
- Based in Bangalore, Hyderabad and Kuala Lumpur





# Scope of services



Aurigene provides specialized chemistry services, leveraging its discovery engine: this combines biology with flexible deployment of resources to give value-added, IP based MedChem output

- **Medicinal chemistry**
  - Small molecules and peptides
- **Fragment based drug discovery**
  - Collection ~5,000 fragments
- **Structural biology**
  - Gene to structure
- **Pharmaceutical Dev**
  - Phys/Chem characterization, formulation support
- **Scale-up**
  - Process development and tech transfer



# Services Track record



Client	Start Date	Specialty service	5	10	15	20	25	30	35	40	45	50
US company	2004	Chemistry	█	█								
US Large Biotech	2007	Peptide chemistry	█	█	█							
EU Large Pharma 1	2008	Chemistry	█	█	█	█	█	█	█	█	█	█
EU Mid-pharma	2009	Peptide chemistry	█	█	█							
EU Large Pharma 2	2011	Peptide chemistry	█									

- Services partnerships with several large and mid-pharma companies
- Most partnerships have been over a long period (>3 years) with significant scale-up in the relationship
- Specialized chemistry services:
  - Currently around 115 chemists (19% of total scientific strength) work on specialized chemistry services
  - Two of these chemistry programs also yielded novel chemistry leading to patent grants
- Programs also handled in structural biology/ crystallography with large pharma partners





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# Medicinal Chemistry





# Broad Chemistry Expertise

- Multi-Step Synthesis
  - Including asymmetric synthesis
- Diversity Oriented Synthesis
  - Scaffold design – pharmacophore modeling
- Organometallic Chemistry (Stoichiometric & Catalysis)
- Atom Efficient Reactions (Pd-, Ni- Catalyzed Reactions, “Click” Chemistry, Multi-component Synthesis)
- Heterocyclic Chemistry
- Asymmetric Synthesis
- Expertise in resolution of racemic mixtures
- A range of cross coupling reactions
- A range of name reactions and FGTs





- Lead Generation Chemistry
  - Compound libraries, designed in-house/customer
  - Typically > 300 compounds/ scaffold
  - 10-25 mg/ compound, ~ 95% purity
- Lead Optimization Chemistry
  - Focused library generation
  - 30-40 compounds/ scaffold
  - 50-100 mg/ compound, ~ 95% purity
- Synthesis of Intermediates
  - 5-10 gm scale, ~95% purity



# Lead Generation strategies



- Analogue design
  - Modifications of existing Active compounds
  - Better drug like properties
  - Intellectual property
- Rational design
  - Molecular modeling
  - Protein sciences: X-ray
  - NMR
- Systematic screening
  - HTS screening Small set of diverse compounds (eg, various heterocyclic scaffolds)





- Homologues:
  - Synthesis of homologues, additional linkers (eg. -C-, -O-, -NH-), isosters, benzologues
- Isomers:
  - Regio isomers, geometrical isomers, Optical isomers
- Ring modifications:
  - Ring Opening, Closure, Expansion, contraction, conformational restriction (Bicyclic rings)
- Effect of substitution:
  - Electronic, steric and lipophilic properties
  - Metabolism





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# Peptide Chemistry





- Peptide Design
- Peptide Synthesis:
  - Manual and automated synthesis
  - Solid and Solution Phase synthesis
  - Mg to multi-gram scale
- Peptide Chemistry
  - Linear and branched chain
  - Derivatised peptides: Derivatisation of Lipids / Steroids / Small molecules/ Carbohydrate Conjugated to peptides
  - Conformationally constrained peptides: Lactams, Multiple disulfides, Stapled peptides
  - Labeling – Biotin; Fluorescein
- Route Scouting and Process Development for multi-gram scale Deliverables

## Scale of synthesis of peptides delivered:

- Peptides
  - Peptides with ~ 50 amino acids
    - 1 g at 95% purity
  - Peptides with ~ 20 – 30 amino acids
    - 5 g at 95% purity
- Peptidomimetic purification (without HPLC)
  - 800 g at 95% purity
- Elemental analysis\*
- Amino acid analysis \*
- CD\*
- MALDI\*



# Complex Peptides Expertise



- ❑ Long and Branched chain peptides
- ❑ Conformationally constrained cyclic peptides
  - Cysteine and Lactam bridging
  - Stapled peptides
- ❑ Phosphopeptides
- ❑ Strategies to improve pK properties:
  - Lipidation, PEGylation
  - Peptides with bioisoesters
  - Steroid derivatisation
- ❑ Labeled peptides
- ❑ Masked peptide aldehydes
- ❑ Peptide based affinity ligands
- ❑ Peptidomimetics
- ❑ Lipids: Phospholipids, cholesterol-lipid conjugates, Lipid phosphates





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# Scale-up and Process Chemistry



# Process chemistry expertise



- Scale up & Process Dev. of lead NCEs for *In-vivo*, PK and Probe-Tox studies
- Process development and scale-up of vital intermediates and scaffolds
- Synthesis of Tool/Standard compounds
- Resolution of racemic mixtures
- Synthesis of: Metabolites, Prodrugs, Stable labeled NCEs
- Salt selection/synthesis
- Polymorph screening/synthesis
- Differentiated products
- Technology transfer to plant scale for clinical supplies



# Track Record : Process Development



## Process Development and scale-up of NCEs

- Process for about 40 NCEs developed to scale them up to 2 kg to support till Probe-Tox studies.

## Process Development and scale-up of vital Intermediates and scaffolds

- New methods for about 30 synthetically challenging intermediates were developed to scale them up for Med. Chem. Group.

## Alternative synthetic route

- New synthetic routes to about 10 NCEs were developed during scale-up

## Metabolite synthesis

- Major metabolites (hydroxy and hydroxymethyl) of 5 NCEs (phase-1) were synthesized

## Prodrugs

- Prodrugs of 3 anti-inflammatory and 1 anti-infective NCE were synthesized

## Resolution of racemic mixtures

- Led to many NCEs. Two differentiated products were discovered for COPD after resolving racemic mixture of known APIs.

## Stable labeled NCEs

- 4 Stable labeled ( $^{13}\text{C}$  and  $^2\text{H}$ ) NCEs (in phase-1) were synthesized.

## Salt selection (in all therapeutic areas)

- Suitable organic and inorganic salts of about 10 potent NCEs were prepared to get the maximum exposure.

## Polymorph screening

- A preliminary polymorph screening for all the NCEs before Probe-Tox to produce most stable morph. Detailed polymorph screening for the NCEs/APIs heading beyond clinical phase-2.

## Technology transfer

- Tech-packs and know how of about 20 NCEs, selected for GLP-Tox & phase-1, were transferred for 5-10 kg c-GMP production





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# TruFrag (FBDD) Structural Biology & Crystallography



# TruFrag™ platform– Introduction and offering

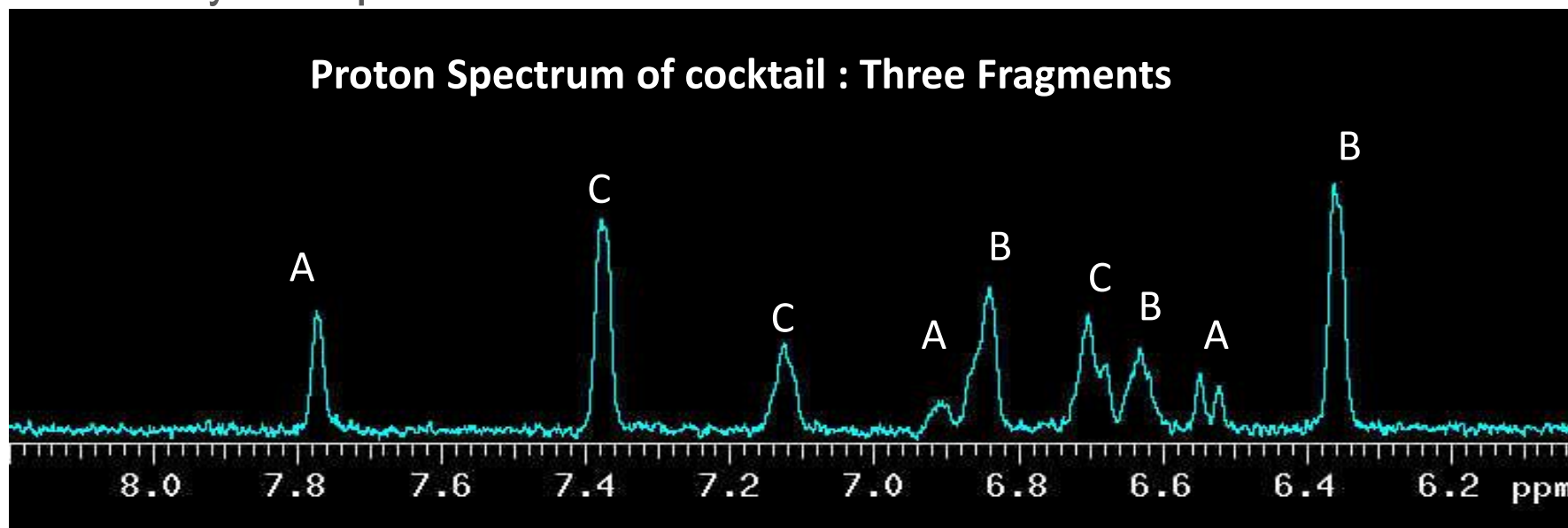


- Aurigene's TruFrag™ platform is an integration of biophysical and computational methodologies into a differentiated approach for fragment based drug discovery
- The TruFrag™ platform offers:
  - Access to a high quality fragment library providing strong starting points for optimization
  - Validated approach integrating protein production, NMR based screening, X-ray crystallography and computational chemistry for fragment based hit generation
  - Lead generation package using the established capabilities of medicinal chemistry, biochemistry and cell biology





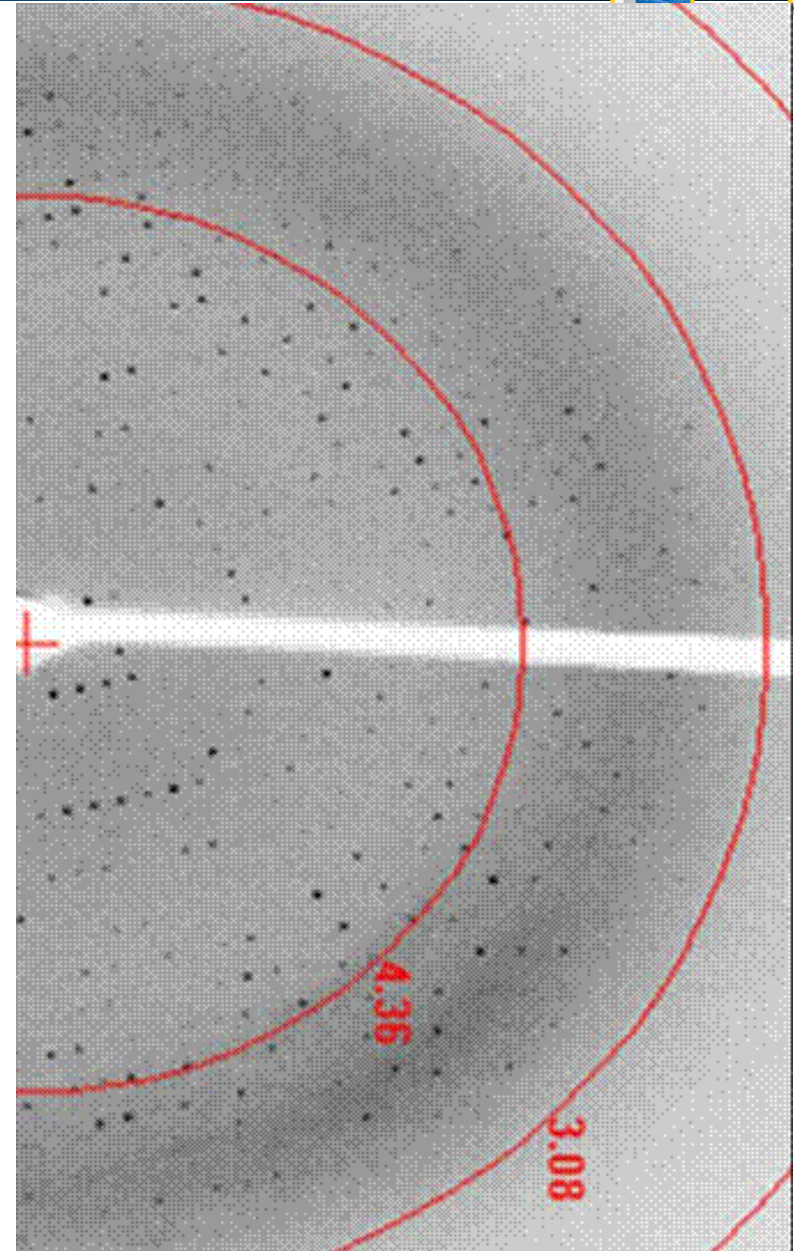
- Fragment Library : Diverse fragment library (5,000+ fragments)
- Follows Rule of 3
  - Molecular weight (150 to 250)
  - $\text{clogP} \leq 3$
  - The number of hydrogen bond donors and acceptors ( $\leq 3$ )
- Solubility  $> 500\mu\text{M}$



# TruFrag: Leveraging Structural Biology



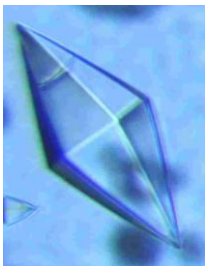
- Protein Expression and Purification
  - Cloning and Expression
  - Purification, Assay Development and Crystallization
- X- Ray Diffraction
  - Crystallization by multiple techniques
  - Structure Determination
    - MIR, MR, MAD etc
    - 210 Structures solved till date
- NMR based Studies
  - Identification of low Affinity binding
    - Water LOGSY, STD
  - Isotopic labeling and partial structure determination
- Computational Capabilities
  - Correlate structure activity relationship (SAR)
  - Pharmacophore modeling
  - *In-silico* screening
  - Simulation of DMPK properties



# Crystallography



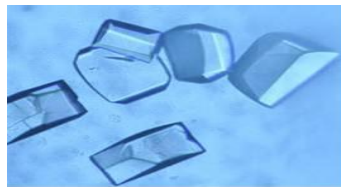
**Kinase**



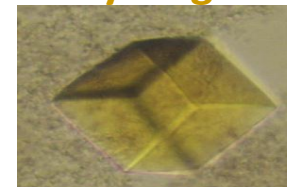
**Protease**



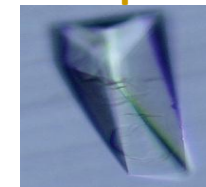
**Nuclease**



**Dehydrogenase**



**Receptor**



**Transcriptional activator**



**Kinase**

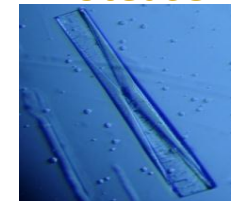


**>280 crystal structures solved**

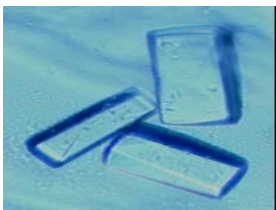
**Kinase**



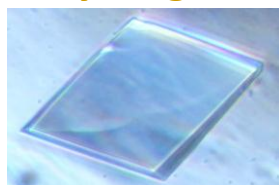
**Protease**



**Nuclease**



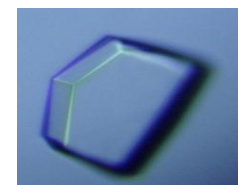
**Dehydrogenase**



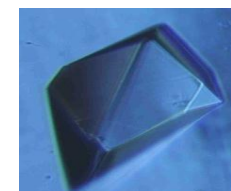
**Carrier protein**



**Kinase**



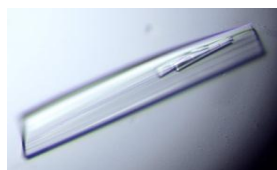
**Oxido-reductase**



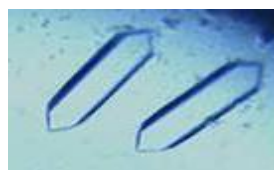
**Kinase**



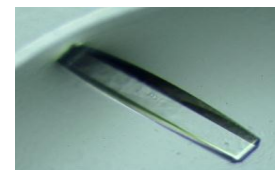
**Kinase**



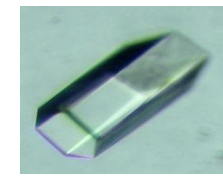
**Nuclease**



**Phosphatase**



**Phosphatase**



# Case Study:

## ATP competitive inhibitor for Aurora kinase

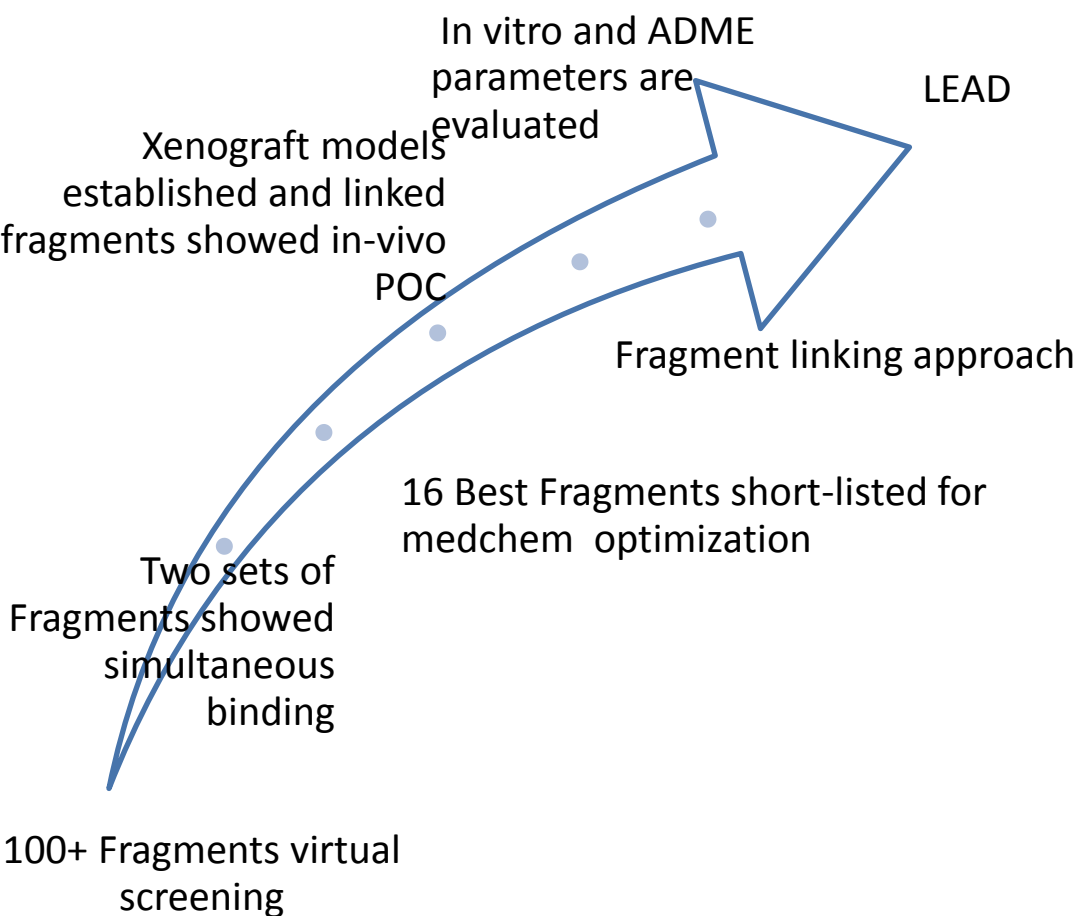


- To identify and develop potent inhibitors of Aurora kinases
- To identify patentable lead compounds
- To establish in vivo proof of concept in cancer models
  
- Success criteria: (Project timeline- 12 months)
  
- Lead compound with the following parameters:
- Molecular Weight  $\leq 550$
- Lead compound to follow Lipinski Rule
- $IC_{50} \leq 0.05\mu M$
- in-vivo POC
- Novel IP

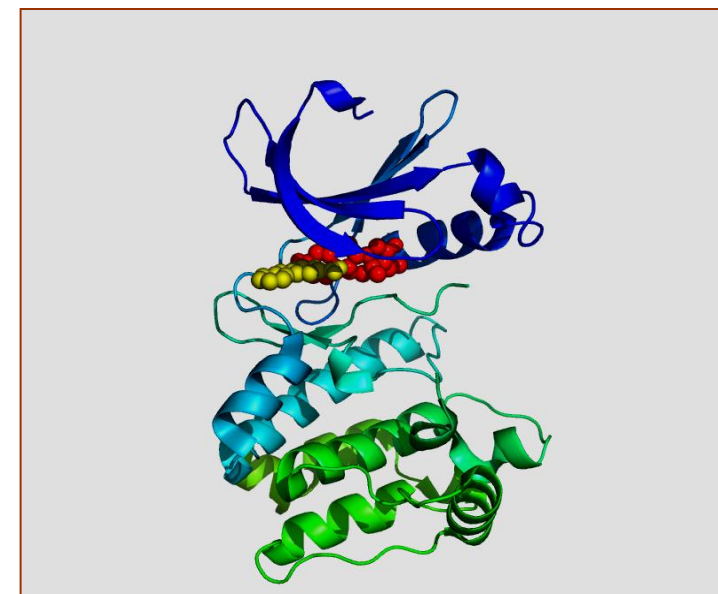




# Case Study: TruFrag™ Approach and Outcome



- ❖ **100+** Fragments screened with following outcome;
- ❖ **16** Fragments were shown to good binding
- ❖ **Two** sets of fragments were showed to bind simultaneously
- ❖ **K<sub>d</sub>: 500μM-1.5mM** for Initial fragment
- ❖ **500-fold** improvement in kinase inhibition
- ❖ *In-vivo* POC was established with the linked fragments to generate a Lead





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# Pharmaceutical Development





## Physicochemical

1. Structure-based prediction of oral \druggability/absorption
2. Ionization constant (pKa)
3. Partition coefficient (Log P)
4. Distribution coefficient (Log D) and Log D versus pH profile
5. Apparent aqueous (DMSO) solubility (for early discovery)
6. Identify potential impact on oral druggability

## Solid-form screen

1. Solid-state characterization of "as is" material
2. Polymorph/ Pseudo-polymorph (phase-specific screen)
3. Salt screening and selection
4. Co-crystals (Usability, stability, pharmaceutical process-ability)
5. Amorphous/ dispersion
6. Selection of preferred/ stable (thermodynamically) polymorph along with process teams
7. Process-induced solid-state transformations

## Bulk & Stability

1. Hygroscopicity classification of compounds
2. Sorption/desorption profile
3. Particle size distribution (PSD)
4. Bulk density; compressibility; flow properties
5. pH stability profile/Accelerated/Stress/Oxidative stability profile
6. Long-term/Accelerated/ Photo/stability (as per ICH)
7. Excipient compatibility studies

## Bio-pharm screen

1. Equilibrium/Intrinsic solubility
2. pH solubility profile
3. Solubility in bio-relevant media (SGF, FaSSIF, FeSSIF)
4. Phase solubility profile (co-solvent, lipids, solubilizers)
5. Dissolution/release profile (Intrinsic/Non-intrinsic)
6. PAMPA/Caco-2 permeability
7. Identify/nominate biopharma-ceutical issues (dissolution rate/ solubility/ permeability)

## Crystallography

1. Crystal structure determination of NCEs/APIs/ impurities using SXRD
2. Configuration of Chiral centre (absolute/relative) enantiomerically pure /racemic
3. Degree of crystallinity
4. Polymorph phase purity
5. Batch to batch reproducibility (PXRD, thermal, intrinsic dissolution)

## Formulation screen

1. Preclinical formulation Screen (Efficacy/PK//Tox formulation)
2. Solubilization/Dissolution enhancement strategies
3. Permeability enhancement
4. Micronization/Nano-sizing
5. Amorphous/Solid dispersion
6. Complexation
7. Lipid-delivery (SEDDS/ SMEDDS/Micro-emulsion)
8. Prototype drug product screen (non-GMP, solid dosage form) for FIH studies



# Track record- Pharmaceutical Dev.



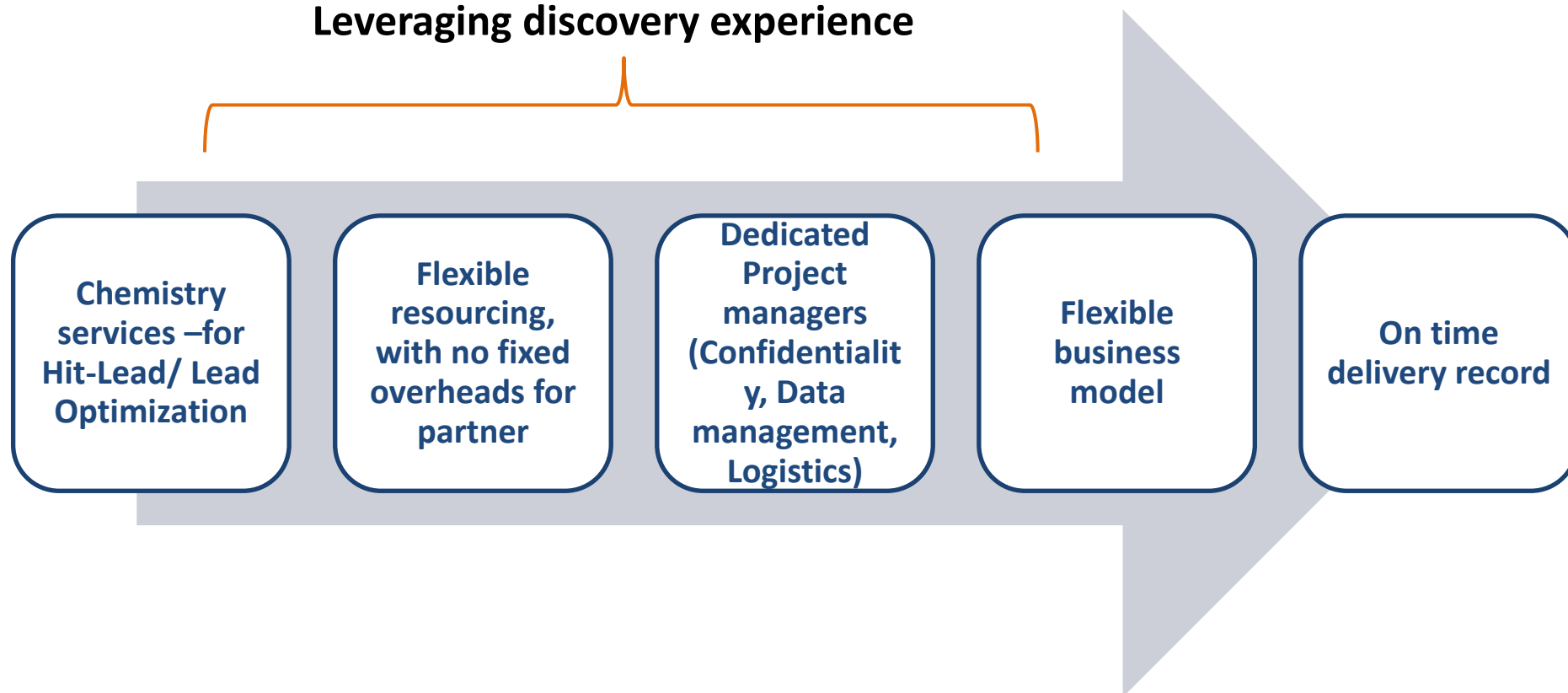
Capabilities	Discovery/Development phase	Track Record
Polymorph propensity assessment/screening	Lead ID phase (preliminary)	>50
	Lead Opt to Candidate nomination or safety phase (preferred morph selection)	>15
	Prior to Phase I and beyond (comprehensive)	5+1
GLP formulation development & support	Formulation development	>25
	Support	>50
Salt screening	Lead ID to phase I	>10
Oral BA issues	Lead ID (early preclinical)	>50
	Lead Opt to Candidate nomination (Preclinical safety)	>20
Pre-formulation package	Pre-CMC (to support candidate nomination)	>20
	Phase I enabling (to support CMC/IMPD filing)	5
Formulation package for phase I prototype product	Prior to phase I (Prototype for FIH)	5



# Aurigene Value Proposition



Leveraging discovery experience



For services collaborations, please write to us at [partnering@aurigene.com](mailto:partnering@aurigene.com)





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Thank you!

