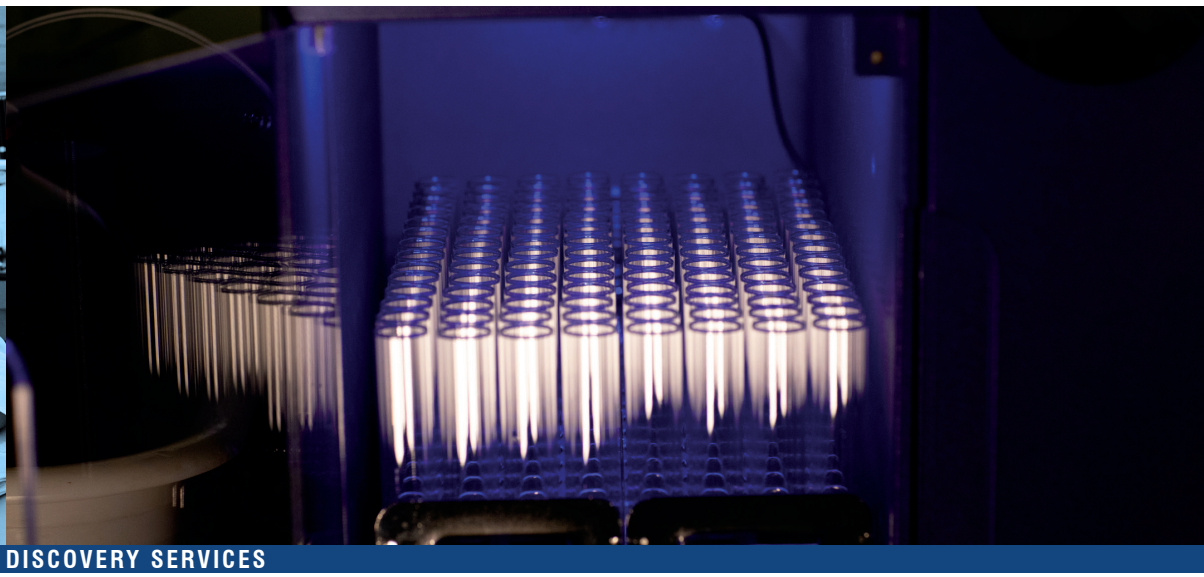
charles river



DISCOVERY SERVICES

Lead Optimization Program Example

As the last phase of the discovery process prior to investment in IND studies, investigators engaged in the lead optimization program bear significant responsibility. Lead optimization demands the broadest level of interdisciplinary cooperation, and a more rigorous approach to translational study design and risk mitigation. In this phase, in addition to optimizing the lead compound's safety profile, researchers must develop a clear understanding of the mode of action and nature of the target, and establish the biological relevance of the animal species used in the pharmacological assays, as well as explore potential differences between animal models and humans[1]. Completing this phase quickly with the necessary information to move confidently into an IND study requires a diverse group of experts working to the same goals, with a shared commitment to actionable data and reproducible results. Cohesive, experienced leadership across a multidisciplinary team can be challenging to achieve, but is key to a program's success. Charles River teams have a demonstrated a winning track record in conducting lead optimization programs, and have delivered 78 development candidates to our partners since 2001.

Lead optimization – a partial list of assays and characteristics under improvement in this phase:

- Potency distribution showing structure-activity relationship (SAR)
- Mechanism of action
- Appropriate LogP and LogD profiles
- Biochemical and functional potency
- Acceptable biochemical kinetics (on-off rates)
- Target engagement *in vitro*
- Selectivity profiling and optimization
- Solubility profiling and optimization
- Permeability (Caco-2)
- Metabolic liabilities profile
- Human plasma protein binding ≤ 99%
- CYP450 inhibition
- hERG and chronic cytotoxicity screen
- Genotoxic liabilities profile
- Cerep® profile
- *in vivo* PK and ADME profile
- *in vivo* efficacy in appropriate animal models

[1] Mũnoz, LM. *Non-Clinical Contribution to Clinical Trials during Lead Optimization Phase*. Behavioral Sciences 2018, vol. 8, 17 (published online Jan 2018)

EVERY STEP OF THE WAY

Phase	Months 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	Estimate
Biology routine screening																			$1.2-1.4M
Medicinal chemistry																			$2.2-2.4M
CADD support: X-ray crystallography (optional)																			$90,000-100,000
in vitro ADME																			$900,000-1M
DMPK																			$200,000-300,000
Efficacy (TBD based on indication)																			(varies by indication)
Structural biology: X-ray crystallography (optional)																			$45,000-60,000
Project Management																			$350,000-450,000
Total (including optional services)																			**$4.99M-5.71M**
Total (excluding optional services)																			**$4.85M-5.55M**

Please note that the above pricing is an estimated range encompassing a project of typical complexity and duration. Final proposal pricing for the full project or any of the component parts will be determined by multiple factors. We hope this pricing example provides a frame of reference for your convenience, but we welcome a deeper discussion about your project to enable you to make a more informed decision.

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