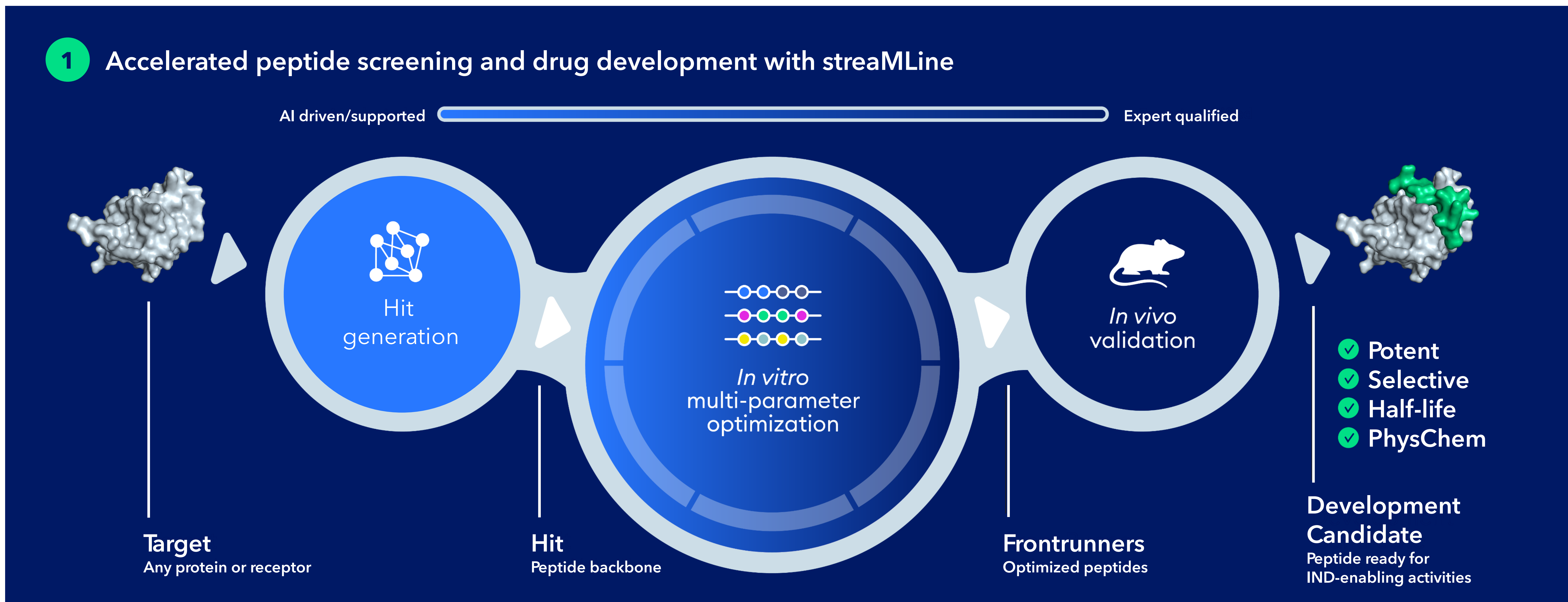


StreaMLine - Machine learning guided development of novel GLP-1 receptor agonists

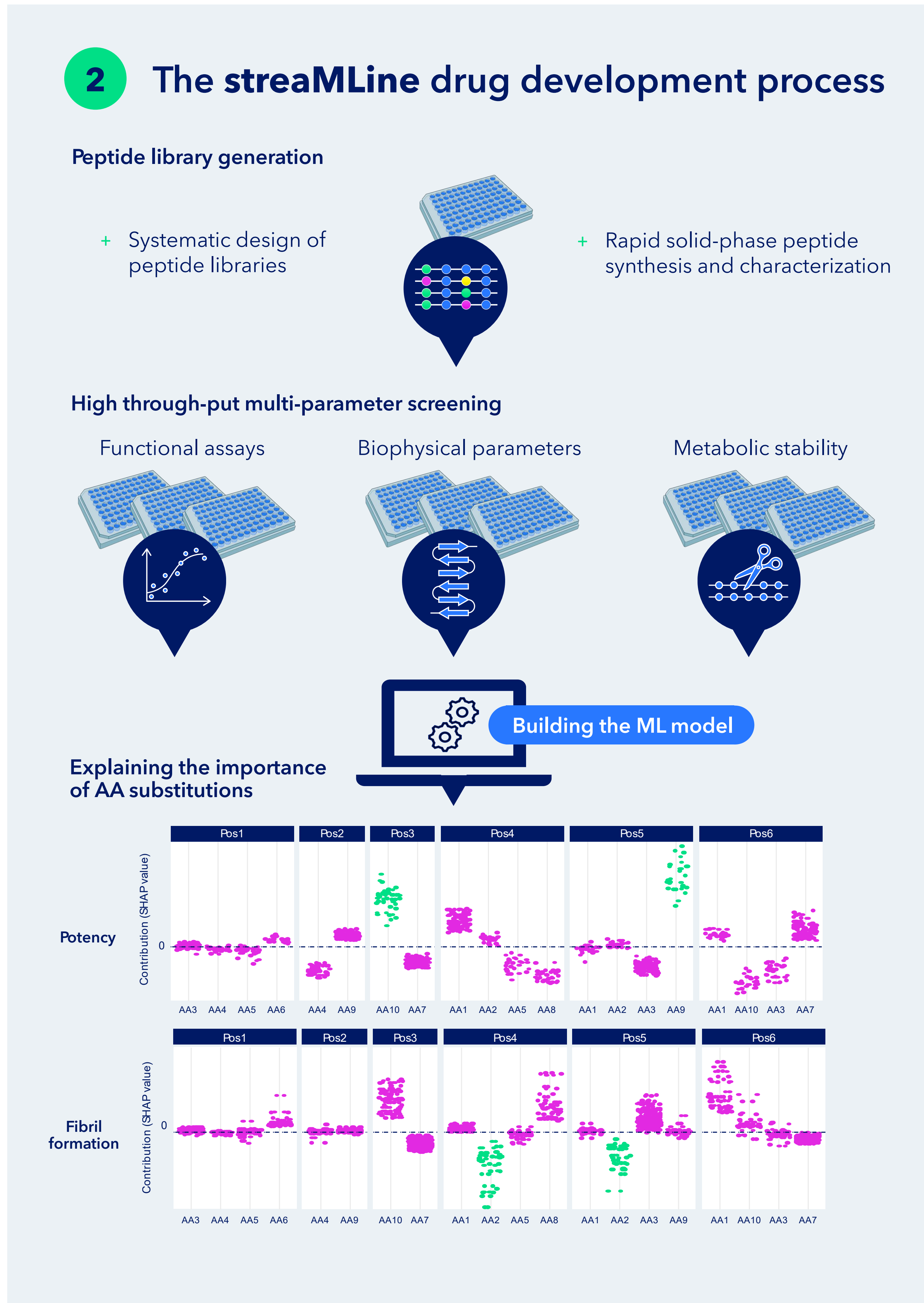
Authors: Claudia Hjerringgaard¹, Jens Christian Nielsen¹, Mads Mørup Nygaard¹, Anita Wester¹, Lisbeth Elster¹, Trine Porsgaard¹, Randi Bonke Mikkelsen¹, Silas Rasmussen¹, Andreas Nygaard Madsen¹, Morten Schlein¹, Niels Vrang¹, Kristoffer Rigbolt¹, Louise S. Dalbøge^{1*}

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1 Accelerated peptide screening and drug development with streaMLine



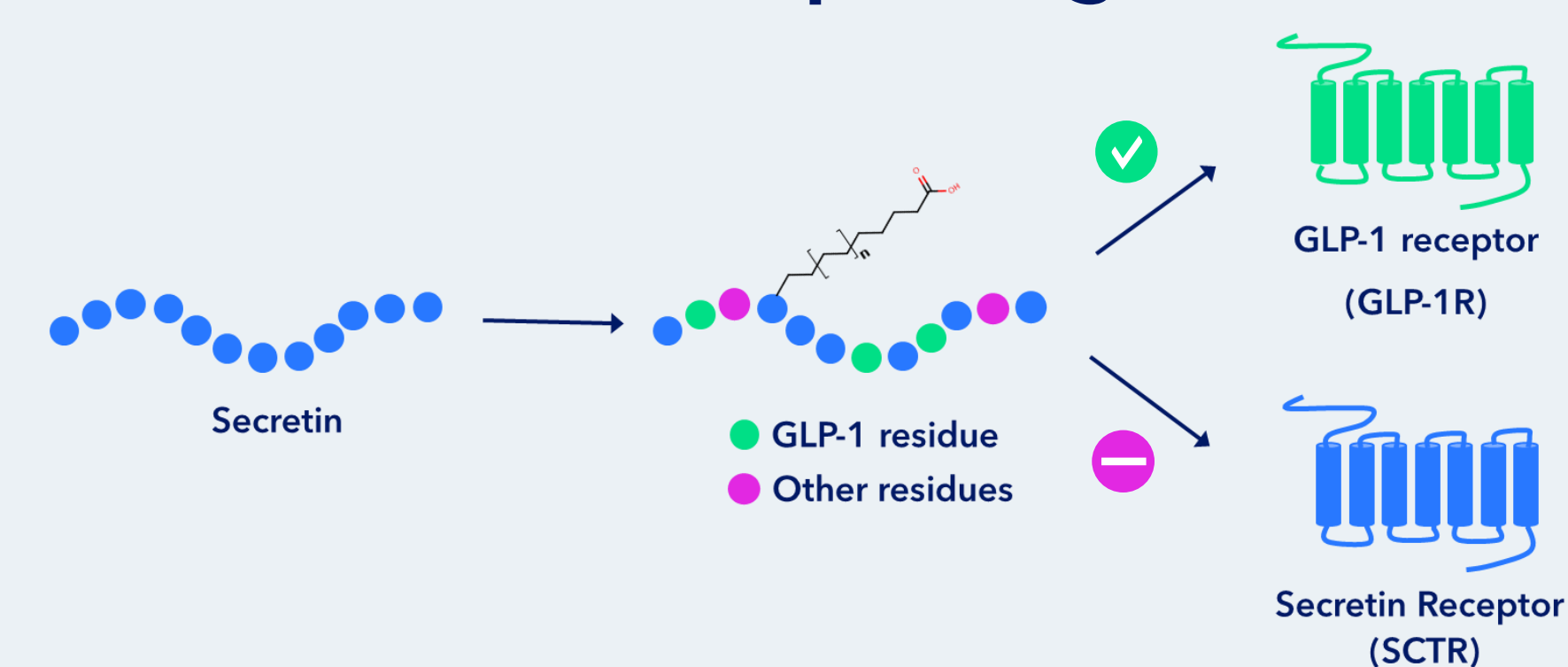
2 The streaMLine drug development process



3 Using streaMLine to make novel GLP-1 receptor agonists

Engineering novel GLP-1 receptor agonist starting from the biophysically robust Secretin peptide

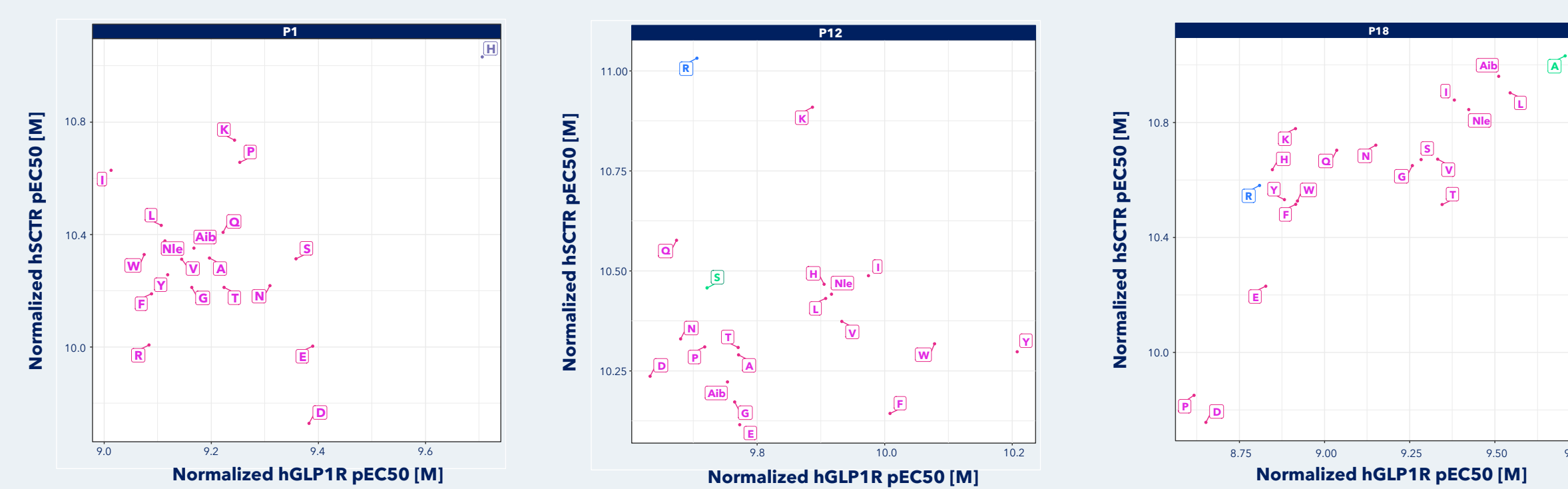
+ **StreaMLine platform** used to screen complete peptide sequence and identify key positions that accurately control GLP-1 receptor selectivity



+ **Parallel optimization of potency, selectivity, biophysical- and pharmacokinetic properties**

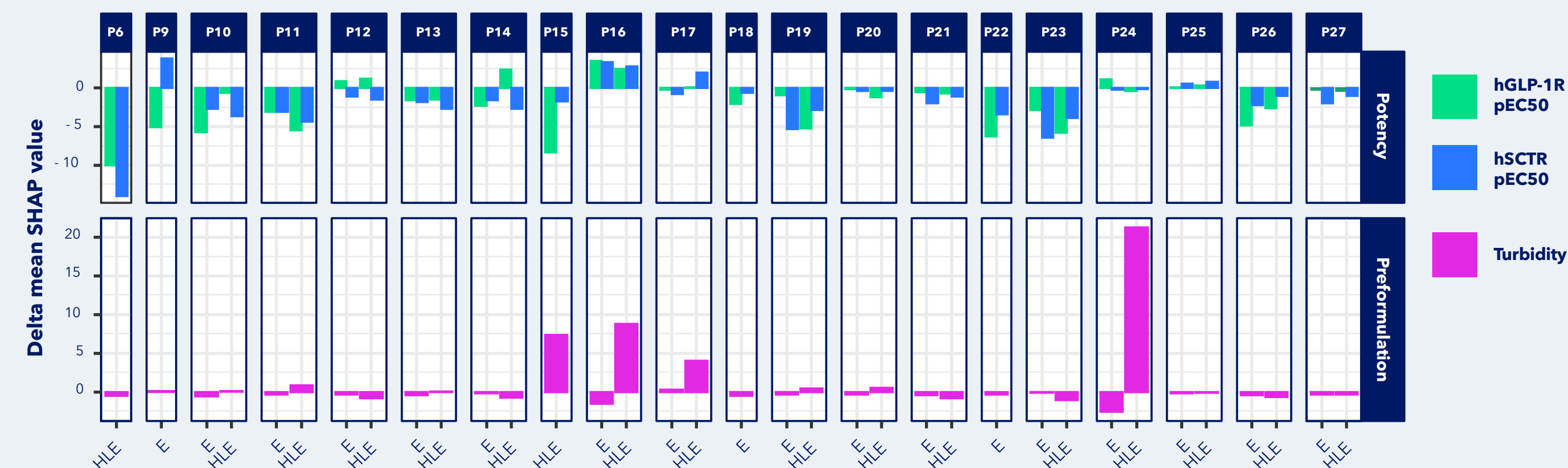
Deep mutational scan

Positional understanding of the peptide backbone



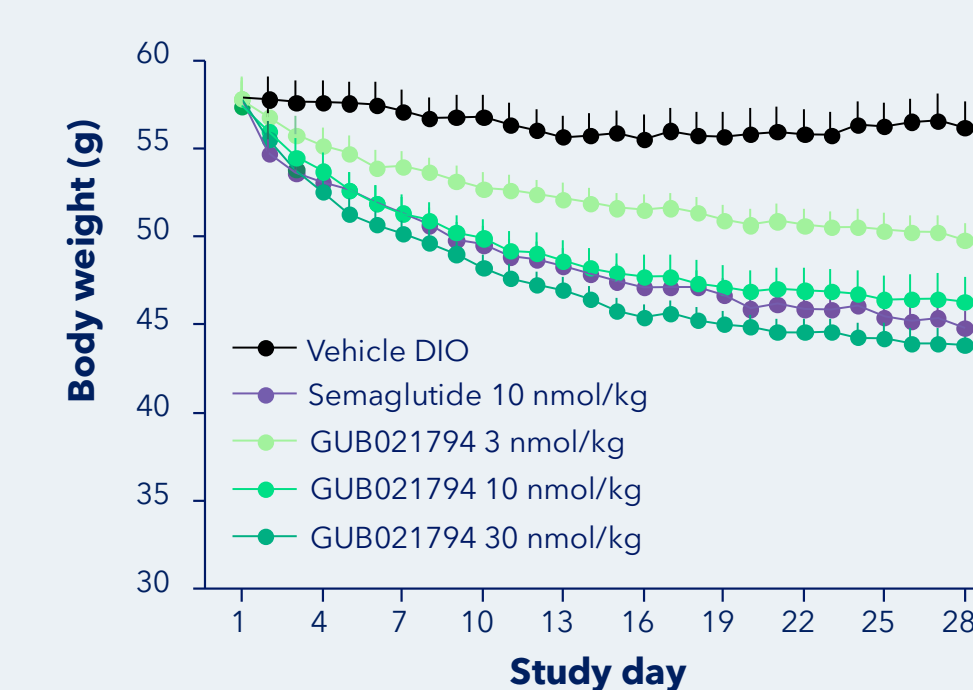
Lipidation (HLE) and glutamate scan

Extending half-life and improving solubility



4 Development candidate characterization

| Compound | hGLP-1R EC ₅₀ (nM) | hSCTR EC ₅₀ (nM) | Solubility, pH 7 (mg/mL) | Chem. stab., pH 7 (% degradation) | Fibrillation, pH 7 (Yes/No) | T _{1/2} , mini pig IV (h) |
|-----------|-------------------------------|-----------------------------|--------------------------|-----------------------------------|-----------------------------|------------------------------------|
| Secretin | 1500 | 0.0025 | - | - | - | - |
| GLP-1 | 0.0022 | 800 | - | - | - | - |
| GUB021794 | 0.019 | 190 | ≥10 | -1.4 | No | 71 |



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