

Integrated Enzyme Technologies

- Integrated group of biologists, computational and process chemists providing expertise ranging from enzyme discovery to commercial bio-processing
- Rapid enzyme library generation and screening
- Enzyme engineering
- Enzyme formulation development and immobilisation
- Strain and synthetic pathway engineering
- Fermentation development and scale-up
- Commercial enzyme supply

• **selectAZyme™**



At Almac, we have the expertise and capabilities to develop novel enzyme technologies and deliver enzyme and chemical products at commercial scale.

Enzyme discovery at Almac benefits from:

- Access to large novel INSIGHT databases of gene and protein sequences
- Use of a wide range of DNA, genomic and protein sequence analytical tools, as well as evolutionary biology computational tools
- Expertise in building, annotating, and querying biological pathways
- Expertise in the study and catalytic function assessment of protein structures using computational chemistry methods and bioinformatics tools
- Highly experienced bioinformaticians who provide insight of DNA and protein sequences, and structural protein modelling

These capabilities enable us to identify and build unique panels of enzymes to suit your specific transformation within weeks.

Enzyme engineering

Enzyme performance is often increased through mutation of the amino acid sequence. Using computational and directed evolution expertise, we have engineered enzymes for increased selectivity, activity, solvent and inhibitor tolerance and thermal stability.

Computational physics based and machine learning methods allow rational selection of sites for mutagenesis, with wet screening <200 enzymes per iteration:

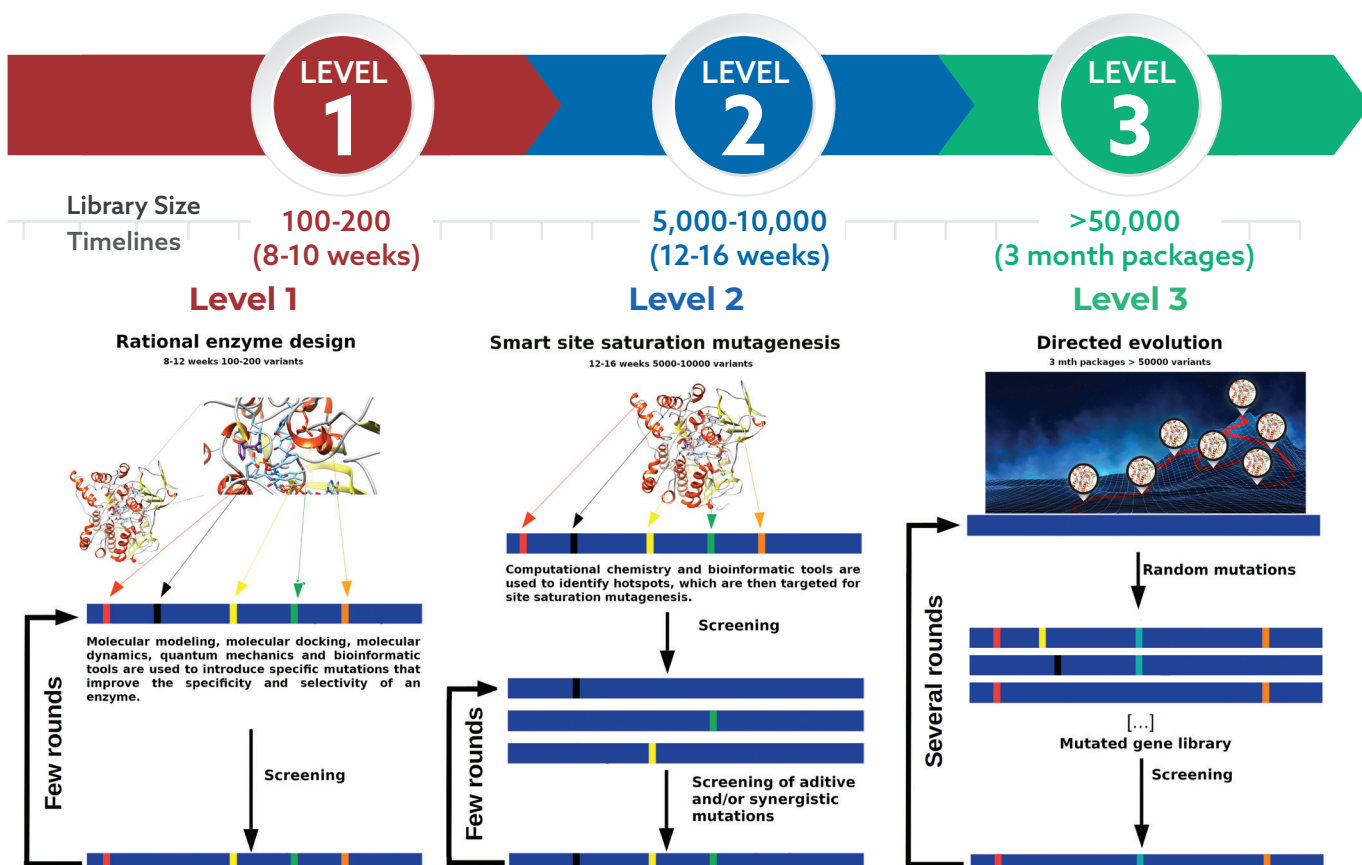
- When required, the fully rational approach is augmented with directed evolution techniques such as site-specific and random mutagenesis
- Parallel UPLC systems allow rapid library screening
- Expertise in expression systems such as *E. coli*, *P. pastoris*, *Streptomyces* and *S. cerevisiae* enables delivery of enzymes for a wide range of applications

Enzyme manufacture

With extensive experience in fermentation, we can optimise the fermentation protocol for your specific process to obtain kilogram to tonnes of enzyme. Our enzymes can be tailored for your process by our dedicated team:

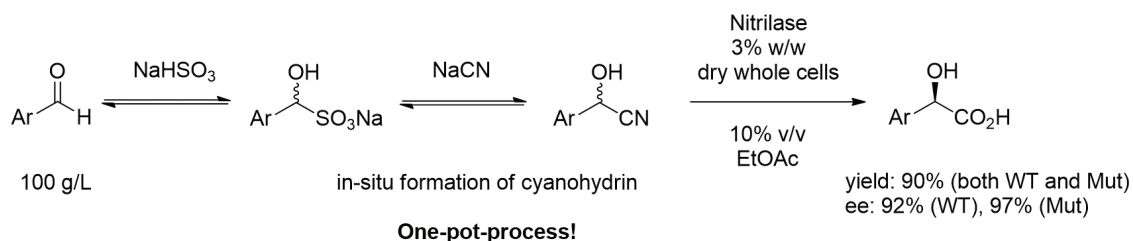
- Fermentation development from shake flask to fed-batch fermentation in weeks
- High level of expertise in optimisation of fermentation and downstream processing
- Fermentation capabilities in-house from 0.1 L to 125 L, and up to 15 m³ via CMO partners
- Formulation in multiple physical forms: lyophilised (freeze-dried) or liquid cell-free lysates, spray-dried whole cells and immobilised cells.

Our approach to engineering:



Case studies

Case study 1 - Process development and enzyme engineering for DKR process:



Our client required improvement of an enzyme mediated synthesis of (R)-2-methoxy mandelic acid to become fit-for-purpose.

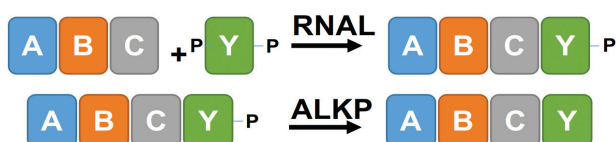
Almac's solution involved rational enzyme and process design to improve product quality and cost. A one-pot process was implemented without need for cyanohydrin

intermediate handling, which also boosted enzyme activity. Enzyme engineering enabled a yield of 90% and ee of 97% with the best variant.

Value for client:

Shorter and less hazardous manufacturing process. Lower product cost and higher product quality.

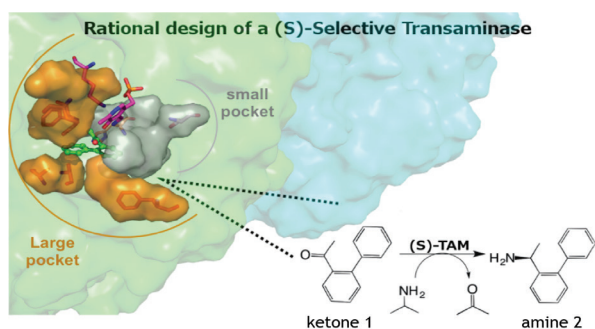
Case study 2 - Discovery and engineering of a RNAL and an ALKP to produce a synthetic single stranded RNA



Client requested the development of a two-enzyme system for synthesising single stranded RNA containing nucleosides with distinct 2'-modifications.

- A panel of new RNA ligases and Alkaline phosphatases enzymes was built using Almac's INSIGHT smart enzyme discovery method
- The best alkaline phosphatase enzyme is highly efficient
- The best WT RNAL ligase was then rationally engineered using computational biology methods to obtain variants with enhanced activity
- The best variant shows 100-fold higher activity than the commercially available RNAL ligase 1 T4

Case study 3 - Molecular modelling and engineering of transaminase enzyme



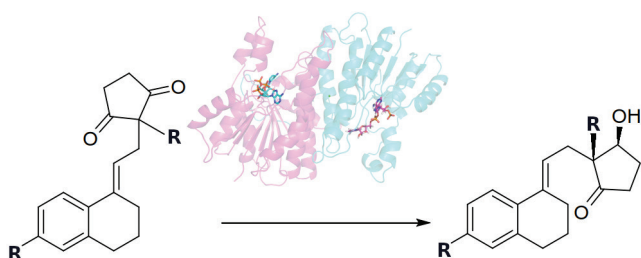
Our client screened the selectAZyme™ transaminase panel for their application and found a hit. However, activity and selectivity required improvement to become fit-for-purpose.

We performed molecular modelling with substrate docking studies to identify key residues for mutations. A panel of variant enzyme was expressed and wet-screened. We were able to increase catalytic activity more than 1716 fold.

Value for client:

Access to active and selective transaminase enzyme for production of a chiral amine.

Case study 4 - Commercial API manufacturing using carbonyl reductase



Client required development of a comprehensive biocatalytic route for API tonne manufacture

The Almac solution involved:

- Development of a novel biocatalytic route to produce the two API compounds
- Enzyme screening and identification of CRED enzyme
- Rational engineering of CRED - computational biology methods were used to design mutants and enhanced activity, thermal stability and solvent resistance
- Reaction and process development
- API pilot- scale production
- Technology transfer for full scale industrial manufacturing

Supporting capabilities

Almac's integrated enzyme technologies can be applied throughout the product lifecycle to guide your synthesis projects from conception to scale-up

Research and development

- Enzyme screening
- Access to selectAZyme™ libraries
- Smart enzyme discovery and engineering
- INSIGHT metagenomics enzyme discovery
- Machine learning assisted enzyme discovery and engineering
- Directed evolution enzyme engineering
- Strain and pathway engineering
- Biotransformation process development
- Enzyme immobilisation development

Process intensification and manufacture

- Ultrasound assisted biotransformation technology
- Integrated chemical manufacture of intermediates
- Immobilised enzyme supply
- Intermediate and active ingredient supply

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