



Codex™ Panels

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- Functionally diverse biocatalyst variants *pre-tuned*...
 - to accept wide range of substrates
 - to produce different stereo-isomers
 - to be chemical process robust (stable to organics, thermo-stable)
 - to be manufactured at commercial scale
- Combinatorial design for sequence-function analysis
- Arrayed on 96-well plates for rapid screening

Advantages to the Process Research Chemist

- Quickly determine feasibility of a biocatalytic route
- Reduce development timelines for biocatalyst optimization – competitive with chemical process optimization
- Available for in-house screening, or as service provided by Codexis
- Deliver low-cost, scalable, environmentally-friendly routes to chiral products

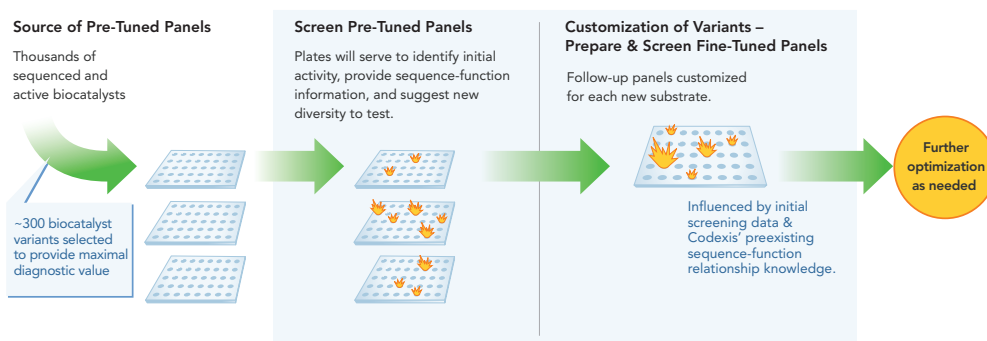
Background: Biocatalysis and Chemical Development

Of the existing techniques available for generating chiral molecules, biocatalysis is the most cost-effective and environmentally-friendly method available. Biocatalysts can perform complex chemical transformations yielding exquisite enantioselectivity under mild conditions and ambient temperatures. However, many of the biocatalysts found in nature have a relatively narrow window of substrate acceptability and demonstrate an inability to perform under commercial chemical manufacturing process conditions (i.e. solvent and temperature stable, substrate and product tolerant). Although traditional methods to improve biocatalytic function have resulted in many commercially successful, high-performance biocatalysts, the time lines required using existing methods have limited the broad use of this technology for pharmaceutical production.

Codex™ Panels: the Next Generation in Biocatalysis Technologies

Codexis now offers sets of its proprietary biocatalysts that are “pre-tuned” to perform under chemical process conditions suitable for pharmaceutical manufacturing, to accept a wide range of substrates, and importantly, to provide sequence-function information that can guide the design of a collection of “fine-tuned” biocatalyst candidates specific for the substrate of interest. The result of this new technology dramatically reduces the development time required to generate a suitable biocatalyst to perform a particular reaction. Now, in a matter of months, process research chemists can move from initial screening of a Codex™ Panel to generating the first kilo quantities of desired material. If required to meet process performance objectives, Codexis can further optimize the biocatalyst using its proprietary directed evolution technology. (For example, refer to Fox, et al., *Nature Biotechnology*, 25, 338-344).

CODEX PANEL OVERVIEW – PRE-TUNED AND FINE-TUNED PANELS



An Integral Tool for the Process Research Chemist

Codex™ Panels are currently offered or in development for five enzyme classes and can be used for producing the following types of molecules:

| Enzyme Class | Typical products |
|--|---|
| Ketoreductases (Codex™ KRED) | Chiral alcohols |
| Acyases (Codex™ Acylase) | Chiral amines or alcohols via resolution of amides or esters |
| Ene reductases (Codex™ ERED) | α and/or β chiral ketones, esters and nitriles |
| Transaminases (Codex™ ACY) | Chiral amines |
| Halohydrin dehalogenases (Codex™ HHDH) | Chiral halohydrins, cyanohydrins, amino alcohols, epoxides, diols |

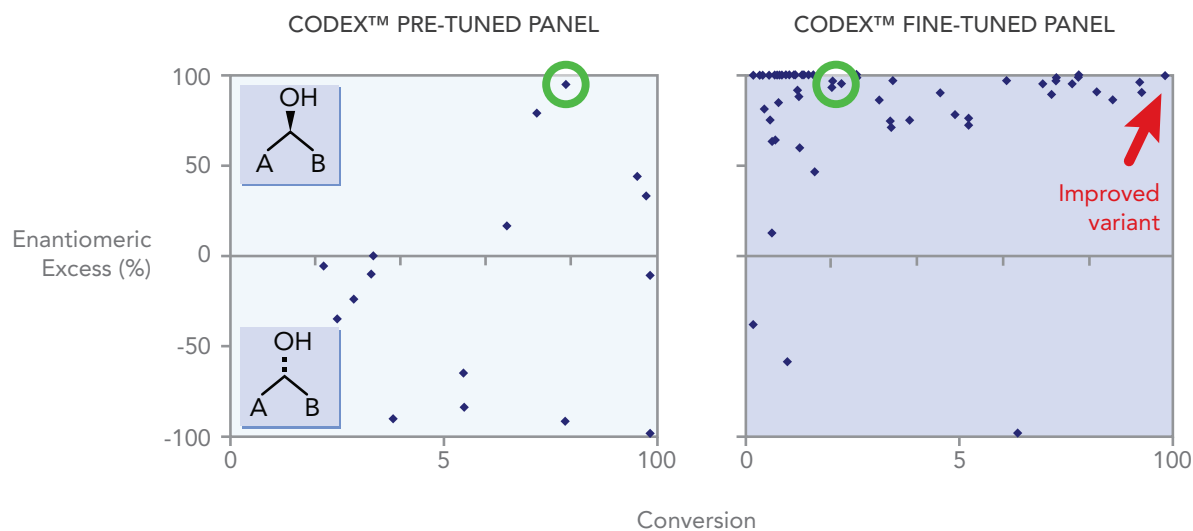
Codex™ Panels can be integrated at an early stage in pharmaceutical process research, when searching for an initial route to generate gram quantities of material for a particular project. Codex™ Panel biocatalysts can often generate >95% ee for a desired chiral product, and can be quickly scaled to enable initial process research to be conducted. When a project advances and more material is required to be generated at higher efficiencies, information gained from the Codex™ Panel can be used to generate “fine-tuned” biocatalysts with higher activities

and enantioselectivities. When commercial quantities are desired, the biocatalyst can be further optimized to generate, in many cases, ~100% ee at 100-200g/L substrate loading with as low as 1g/L enzyme load. Codex™ Panels can be shipped to the pharmaceutical process research chemist to enable in-house screening. Each panel consists of one to three 96-well plates containing cell lysates: simply add substrate, solvent, co-factor (if necessary), allow the reaction to proceed and assay for desired product. Alternatively, Codexis can perform the screen and provide the results.

Proven Success

Codex™ Panels have been applied to a number of commercially-relevant projects. Below is an example of a program using the Codex™ KRED Panel. A large-scale screening effort at a pharmaceutical company showed no existing ketoreductase with desired activity and screening of natural enzymes at Codexis similarly did not reveal the desired activity. However, screening

of the Codex™ KRED Panel identified multiple variants that had a range of enantioselectivities and activities. Based on the sequence-activity data from the pre-tuned panel, a new plate of variants was designed and customized for this particular chemical process. Many of the resulting fine-tuned biocatalysts showed marked increase in enantioselectivity and activity.



Codex™ Panels identify biocatalysts with high enantioselectivity and activity: Circles denote the best variant from the Pre-tuned Panel used as a control for the Fine-tuned Panel. The Fine-tuned panel was screened under more demanding conditions to easily identify improved variants. Arrow denotes an improved variant showing exquisite enantioselectivity that nearly converts all of the substrate.