CODEXIS®

Codexis' Approach to Bio-Based Chemicals

Bio Pacific Rim

Lori Giver, V.P. of Systems Biology, Codexis, Inc.

October 10, 2012

Outline

- Codexis Company Background
- State of the Art and Gaps – Bio-produced Chemicals
- Single Enzyme Evolution Technology
- Creating Novel Production Strains
- Synthetic Biology Technology
- Biofuels and Bioderived Chemicals

Forward-Looking Statements

These slides and the accompanying oral presentation contain forward-looking statements that involve risks and uncertainties. These statements relate to future events or our future financial or operational performance and involve known and unknown risks, uncertainties and other factors that could cause our actual results, levels of activity, performance or achievement to differ materially from those expressed or implied by these forward-looking statements. Forward-looking statements include all statements that are not historical facts. In some cases, you can identify forward-looking statements by terms such as “may,” “will,” “should,” “could,” “would”, “expects,” “plans,” “anticipates,” “believes,” “estimates,” “projects,” “predicts,” “potential,” or the negative of these terms, and similar expressions and comparable terminology intended to identify forward-looking statements. These forward-looking statements represent our estimates and assumptions only as of the date hereof, and, except as required by law, we undertake no obligation to update or revise publicly any forward-looking statements, whether as a result of new information, future events or otherwise.

Other factors that could materially affect actual results, levels of activity, performance or achievements can be found in Codexis’ Quarterly Report on Form 10-Q filed with the SEC on May 20, 2012, including under the caption “Risk Factors.” If any of these risks or uncertainties materialize, or if our underlying assumptions prove to be incorrect, actual results, levels of activity, performance or achievement may vary significantly from what we projected.

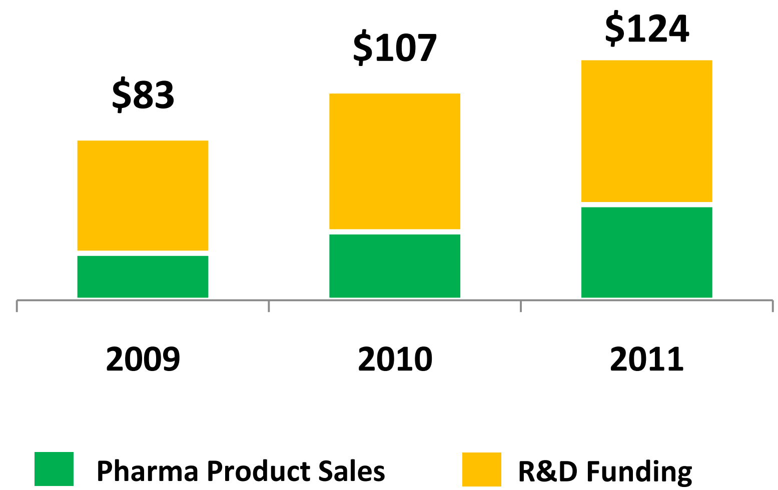
Our logo, “Codexis,” and other trademarks or service marks of Codexis, Inc. appearing in this presentation are the property of Codexis, Inc. This presentation contains additional trade names, trademarks and service marks of other companies. We do not intend our use or display of other companies’ trade names, trademarks or service marks to imply relationships with, or endorsement or sponsorship of us by, these other companies.

About Codexis

We develop enzymes and microorganisms that enable cost-advantaged production of biofuels, bio-based chemicals, and pharmaceuticals

- **Founded 2002**
- **Powerful, proprietary technology enables next generation biofuels and consumer products**

Revenue, $M's



Our Core Assets

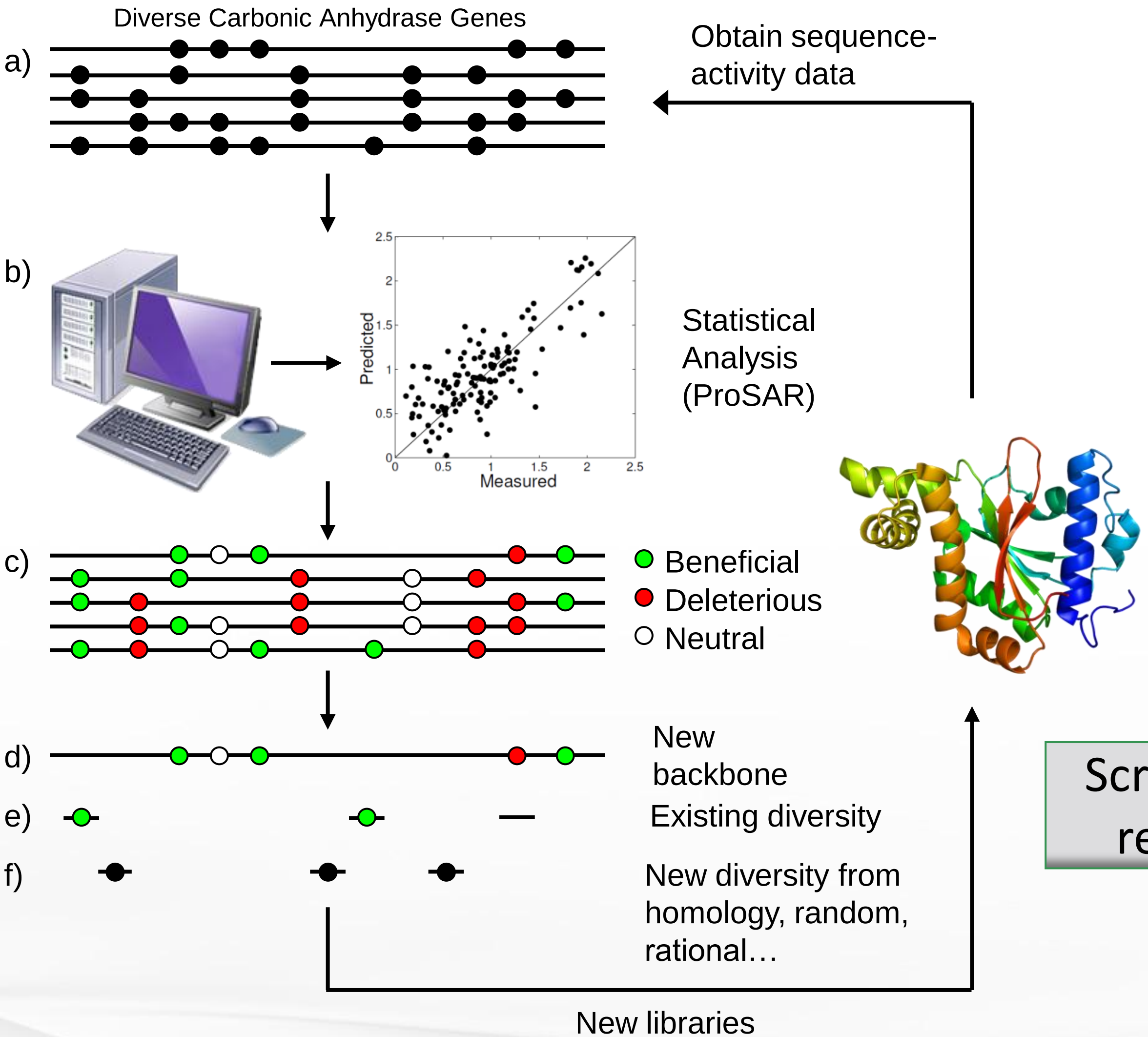
CodeXyme™ Cellulase	CodeXol™ Detergent Alcohol	Pharma
Enzymes to Enable 2nd Gen Fuels and Chemicals	Bio-Based Chemicals For Consumer Products	Established, Growing Pharma Business

CODEXIS®

EVOLUTION OF ENZYMES WITH NON-NATURAL ACTIVITY

CODEXIS®

Codexis Directed Evolution Technology



Screen under process-relevant conditions

Fox & Huisman TibTech 2008

ProSAR: Protein Sequence-Activity Relationships:
A statistical model that correlates sequence with function.

amino acid position number

amino acid code letter

Activity	Variable (X)																
	2T	2K	3A	3S	5D	5E	12K	12R	14D	14N	14E	19Y	19M	20L	20P	27N	27Q
6.2	1	0	1	0	1	0	1	0	1	0	0	1	0	1	0	1	0
3.3	1	0	1	0	1	0	0	1	1	0	0	1	0	1	0	1	0
4.7	1	0	0	1	0	1	1	0	0	1	0	0	1	0	1	1	0
8.5	1	0	1	0	1	0	0	1	1	0	0	0	1	0	1	1	0
9.2	0	1	1	0	1	0	0	1	0	1	0	1	0	1	0	0	1
9.8	0	1	0	1	0	1	0	1	1	0	0	1	0	1	0	1	0
1.5	1	0	1	0	1	0	0	1	1	0	0	1	1	0	1	1	0
2.7	1	0	1	0	0	1	0	1	0	0	1	1	0	1	0	0	1
6.4	1	0	1	0	1	0	1	0	1	0	0	0	1	1	0	1	0
3.5	1	0	1	0	1	0	0	1	0	0	1	1	0	1	0	1	0

Predicted output (activity)

Input (mutations)

leads to: $y = c_{2T}x_{2T} + c_{2K}x_{2K} + c_{3A}x_{3A} + c_{3S}x_{3S} + \ldots + c_0$

Regression coefficients (effect on activity)

Coefficients (c values) are determined by linear regression..

Fox *et al.* (2003) *Prot. Eng.*; Fox (2005) *J. Theor. Biol.*;
WO 03/075129; US 2004-0072245

CODEXIS

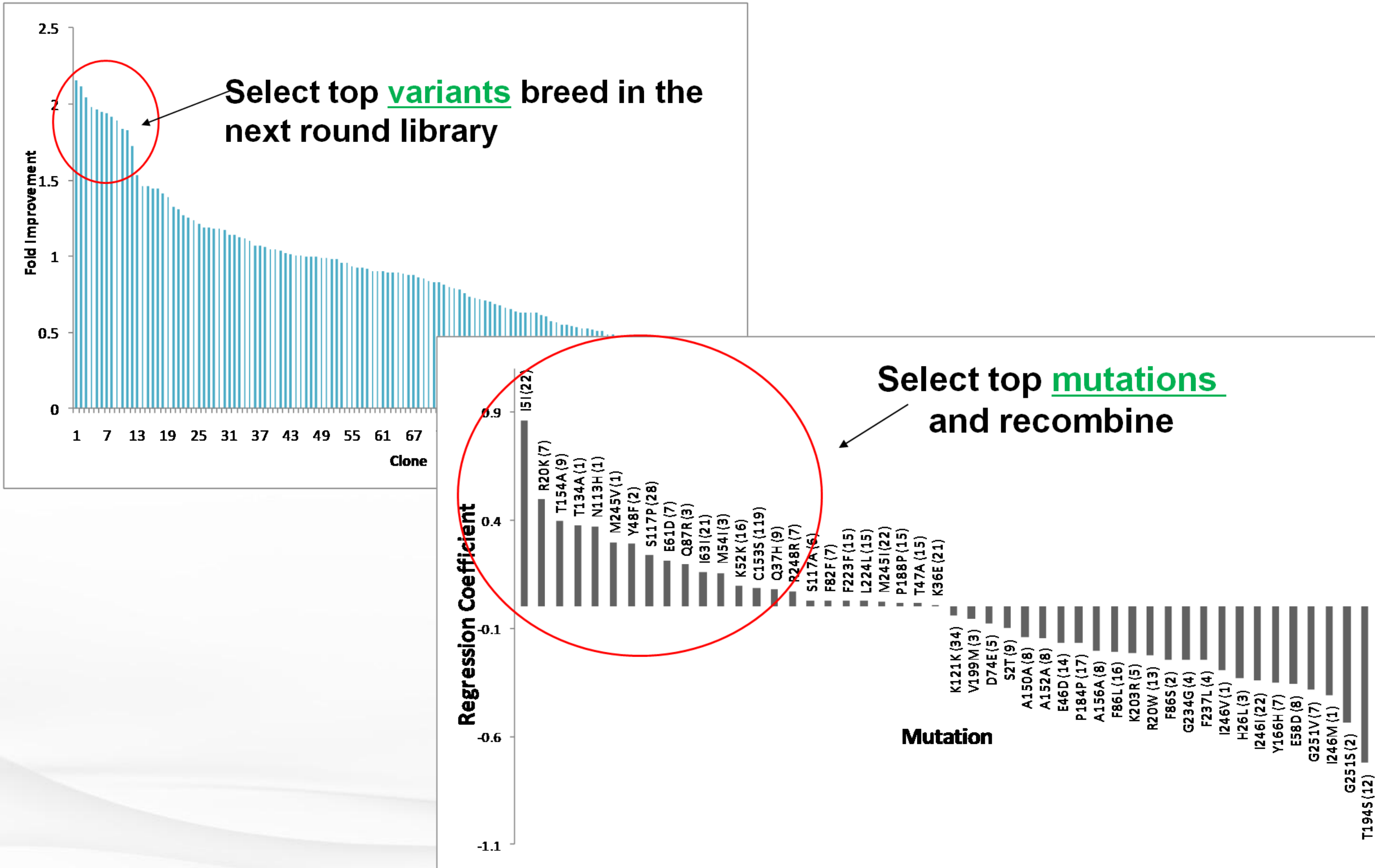
ProSAR Model: Alignment View

Color coded ranking of correlation coefficients

Sample	Acti...	40:14	43:15	76:26	91:31	97:33	106:36	115:39	124:42	130:44	169:57	172:58	181:61	202:68	283:95	337:113	364:122	535:179	571:191	577:193	742:248	898:300	952:318	991:331	1015:339	1018:340	1135:379	1138:380	1150:384	1177:393	1186:396	1195:399	1201:401	1237:413
S01536317	5.26	T	D	I	T	D	K	V	T	E	R	M	T	I	Q	R	I	D	E	P	R	G	G	G	V	P	E	D	G	L	G	L	I	F
S01558855	4.9	T	D	I	T	D	E	V	T	E	R	M	T	I	M	R	I	N	E	P	R	R	G	H	I	P	E	D	G	I	G	L	L	F
S01536357	4.84	T	D	I	T	D	K	V	T	E	R	M	T	I	Q	R	I	D	E	P	R	G	G	G	V	P	E	D	G	L	G	L	I	F
S01536281	4.81	T	D	I	T	D	E	V	T	E	R	M	T	I	Q	R	I	N	E	P	R	G	G	H	I	P	E	D	G	L	G	L	I	F
S01558983	4.66	T	D	I	T	D	E	V	T	E	R	M	T	I	M	R	I	N	E	P	R	R	G	H	I	P	E	D	G	L	G	L	I	F
S01558964	3.65	T	D	I	T	A	E	V	T	E	R	M	T	I	M	R	I	N	E	P	R	R	G	H	I	P	E	D	G	L	G	M	I	F
S01535993	3.61	T	D	I	T	D	E	V	S	D	R	M	T	I	Q	R	M	D	E	P	R	G	G	G	V	P	E	D	D	L	G	L	I	F
S01558741	3.6	T	D	I	T	A	E	V	T	E	R	M	T	I	M	R	I	N	E	P	R	R	G	H	I	P	E	D	G	L	G	M	I	F
S01558975	3.45	T	D	I	T	D	E	V	T	E	R	M	T	I	M	R	I	N	E	P	R	R	G	H	I	P	D	E	G	I	G	L	I	F
S01535862	3.29	T	D	I	T	D	E	V	T	E	R	M	T	I	Q	R	I	D	E	P	R	G	G	G	I	P	E	D	G	L	G	L	I	F
S01558917	3.06	T	D	I	T	D	E	V	T	E	R	M	T	I	M	R	I	N	E	P	R	R	G	H	I	P	E	E	G	L	G	L	I	F
S01535863	3	T	D	I	T	D	E	V	T	E	R	M	T	I	Q	R	I	D	E	P	R	G	G	G	I	P	E	D	G	L	G	L	I	F
S01535889	2.89	T	D	I	T	D	E	V	T	E	R	M	T	I	Q	R	I	D	E	P	R	R	G	G	I	P	E	D	G	L	G	L	I	F
S01535810	2.77	T	D	I	T	D	E	V	T	E	R	M	T	I	Q	R	I	D	E	P	R	R	G	G	I	P	E	D	G	L	G	L	I	F
S01536355	2.7	T	D	I	T	D	E	V	T	E	R	M	T	M	Q	R	I	D	E	P	R	G	G	G	I	P	E	D	G	L	G	L	I	F
S01558825	2.44	T	D	I	T	D	E	V	T	E	R	M	T	I	M	R	I	N	E	P	R	R	G	H	I	P	E	D	G	L	S	L	I	F
S01495533	2.28	T	D	L	T	D	K	V	T	E	R	L	T	I	Q	R	I	D	E	P	R	G	G	G	V	P	E	D	G	L	G	L	I	F
S01536121	2.21	T	E	I	T	D	K	V	T	E	R	M	T	I	Q	R	I	D	E	P	R	G	G	G	I	P	E	D	G	L	G	L	I	F
S01495615	2	T	D	L	T	D	K	V	T	E	R	L	T	I	Q	R	I	D	E	P	R	G	G	G	V	P	E	D	G	L	G	L	I	F
S01495348	1.91	T	D	L	S	E	K	V	T	E	R	M	T	I	Q	R	M	D	E	P	R	G	G	G	V	P	E	D	G	L	G	L	I	F
S01495505	1.86	A	D	L	T	D	K	V	T	E	R	L	T	M	Q	R	I	D	E	P	R	G	G	G	I	P	E	D	G	L	G	L	I	F
S01495628	1.74	T	D	L	T	D	K	V	T	E	R	L	T	I	Q	R	I	D	E	P	R	G	G	G	V	P	E	D	G	L	G	L	I	F
S01495608	1.65	T	D	L	T	D	K	V	T	E	R	L	T	M	Q	R	I	D	E	P	R	G	G	G	V	P	E	D	G	L	G	L	I	F
S01536126	1.54	T	D	L	T	D	K	V	T	E	R	L	T	M	Q	R	I	D	E	P	R	G	G	G	V	P	E	D	G	L	G	L	I	F
S01495273	1.46	T	D	L	S	E	K	V	T	E	R	L	T	M	Q	R	I	D	E	P	R	G	G	G	V	P	E	D	G	L	G	L	I	F
S01495287	1.31	T	E	L	T	D	K	V	T	E	R	M	T	I	Q	R	M	D	E	P	R	G	G	G	V	P	E	D	G	L	G	L	I	F
S01495598	1.29	T	D	L	T	E	K	V	T	E	R	M	T	I	Q	R	I	D	E	P	R	G	G	G	V	P	E	D	G	L	G	L	I	F
S01495541	1.27	T	D	L	S	E	K	V	T	E	R	M	T	I	Q	R	I	D	E	P	R	G	G	G	V	P	E	D	G	L	G	L	I	F

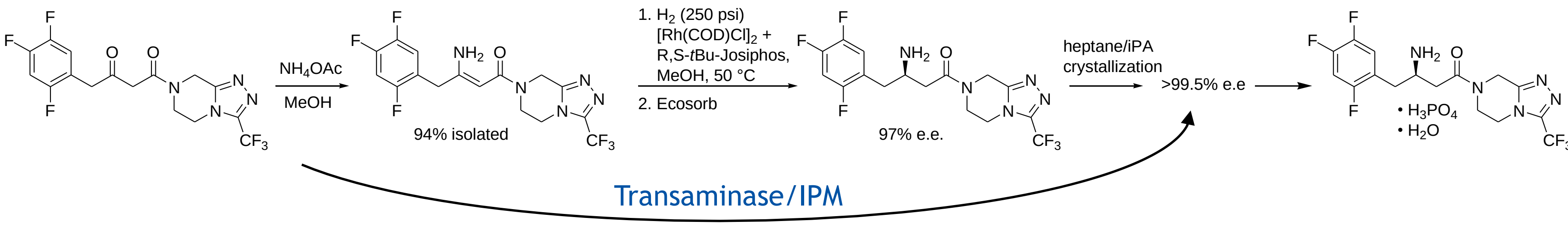
CODEXIS®

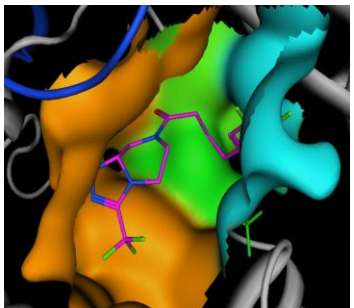
“Hit”-Shuffling vs. ProSAR-driven evolution

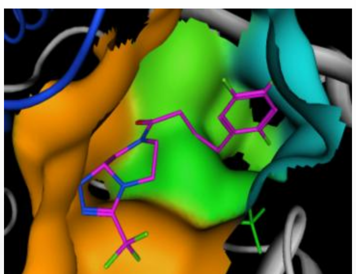


CODEXIS®

A Biocatalytic Route to Sitagliptin




ATA-117 homology model


Model with accumulated pocket mutations

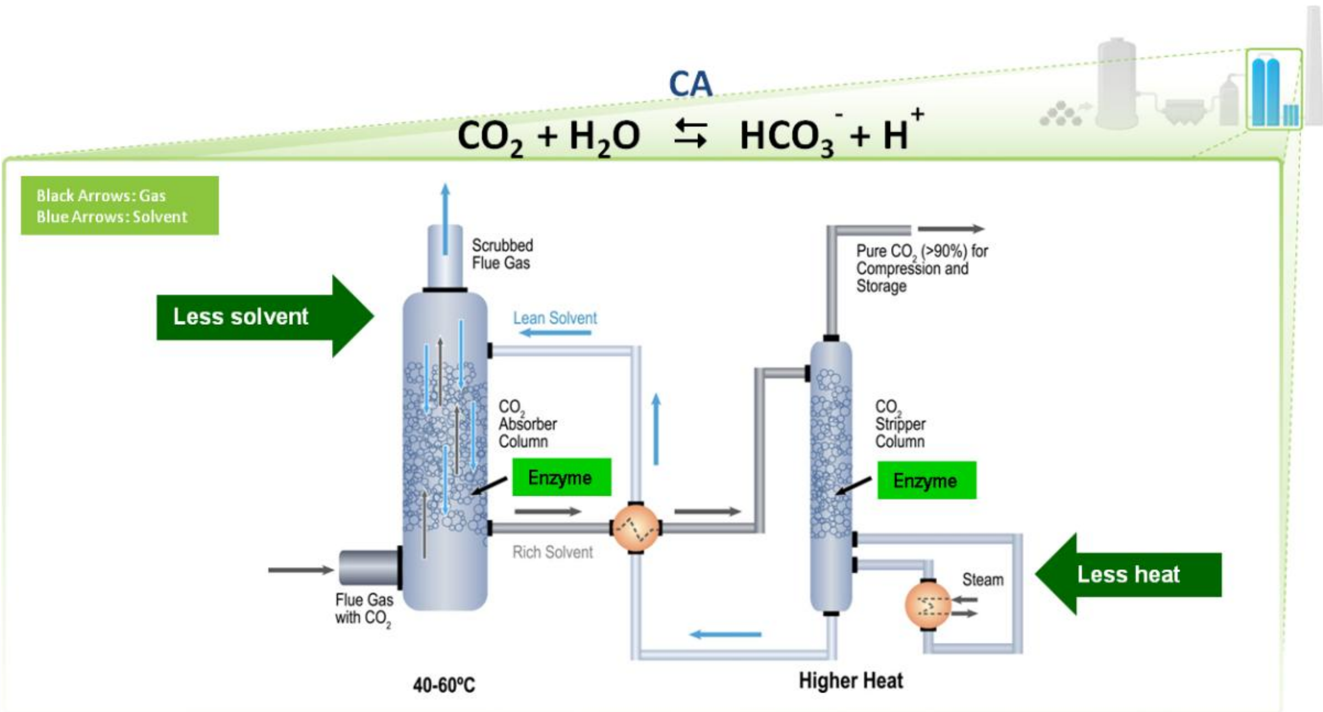
- No natural transaminase had any activity on the prositagliptin ketone,
- ATA-117 showed activity on a truncated analog of the substrate, and this activity was improved 11-fold in first round of evolution.
- Then activity was established on the substrate of interest.
- Further 25,000-fold improvement achieved
- 27 mutations overall
- **Current process: 250 g/L ketone, 50% DMSO, 50^{o}C, pH10**

- **Awarded Presidential Green Chemistry Challenge Award in 2010 with Merck**

▪Awarded 2012 US Presidential Green Chemistry Award with UCLA

Science 2010, 329:305-309

Carbonic Anhydrase Accelerates Energy Efficient Capture Solvents



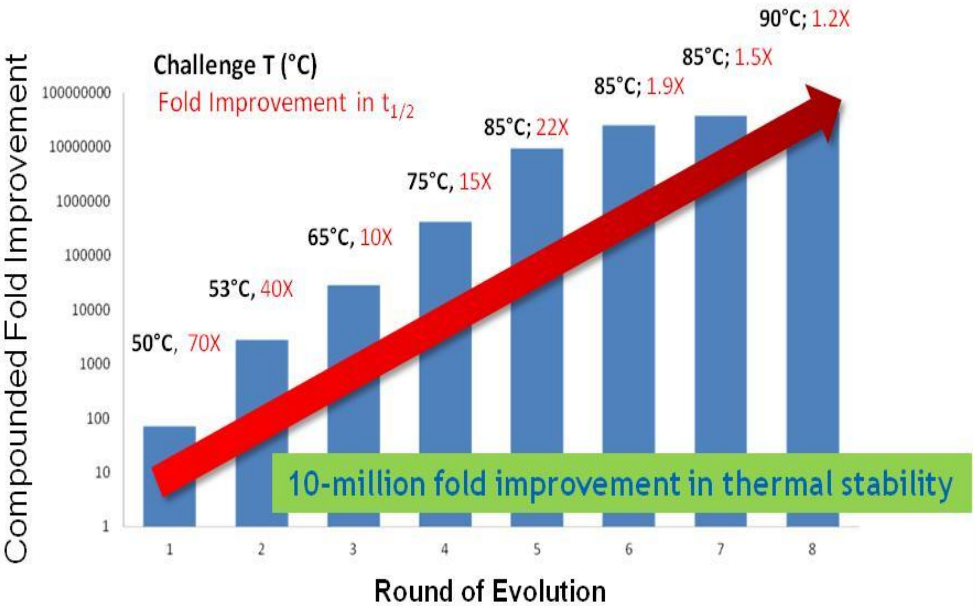
90% reduction in CO_2 absorber column size with low-energy solvent (MDEA)

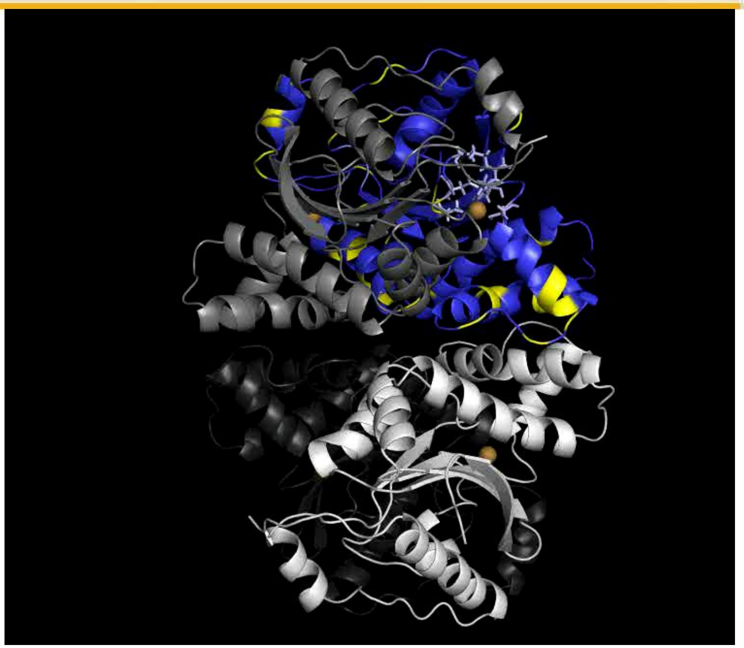
Process requires significantly less heat to release CO_2

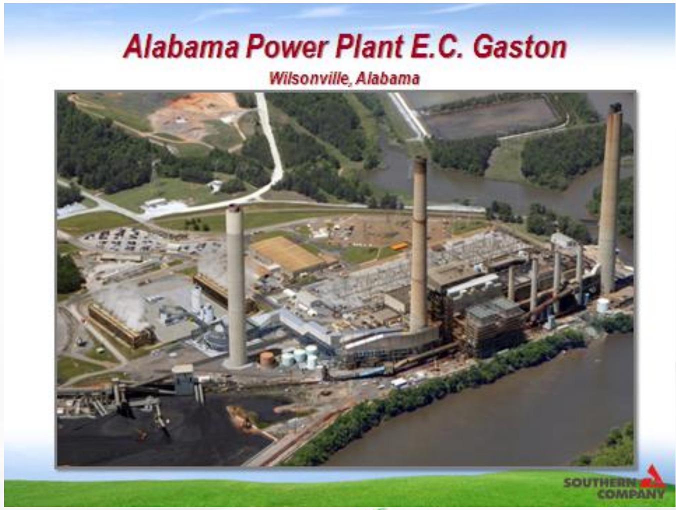
30% lower potential energy consumption than industry standard solvent

Potential savings of $50-70 million / year for typical power plant

Summary of Carbonic Anhydrase Evolution







- Nine rounds of evolution created enzymes with 10^6-10^7 increased stability
- Latest variants stable for 24h in 4.2M MDEA at 92 °C, >3 months at 50 °C
- Latest variant survives 1 h in 4.2M MDEA at 108 °C
- 36 mutations (85% identical to parent)
- Successful pilot trial with real flue gas

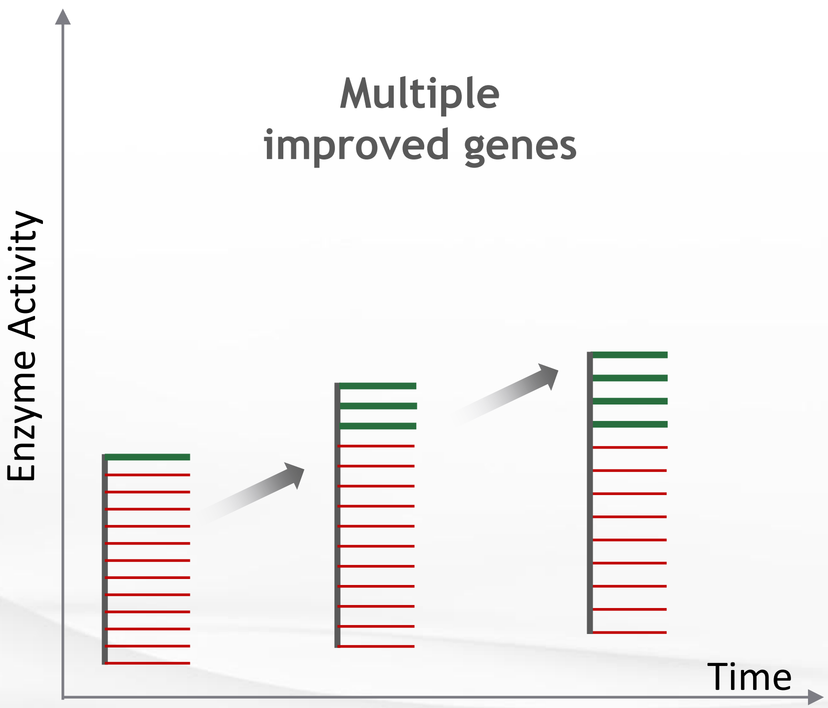
CODEXIS®

CodeEvolver™ Directed Evolution Technology Platform

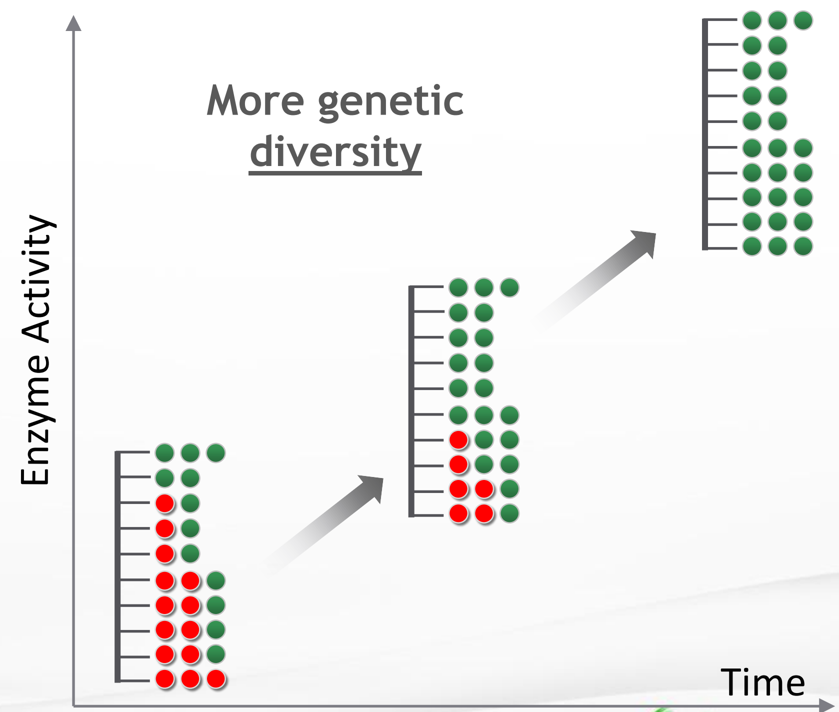
Faster, cheaper synthetic biology enables CodeEvolver™ improvements…

- 2006 atorvastatin (Lipitor®): **4,000** fold in 2½ years
- 2008 sitagliptin (Januvia®): **28,000** fold in 9 months
- 2011 carbonic anhydrase (CCS): **100,000** fold in 6 months

Legacy Shuffling Technology



CodeEvolver™



BIODERIVED DETERGENT ALCOHOLS

Integrated Platform to Produce Fuels and Chemicals from Inexpensive Non-Food Biomass

Biomass	Sugars	End Markets

CODEXIS →

CODEXIS →

Ethanol

Detergent Alcohol

Diesel Fuel

Enzymes
(Biomass → Sugars)

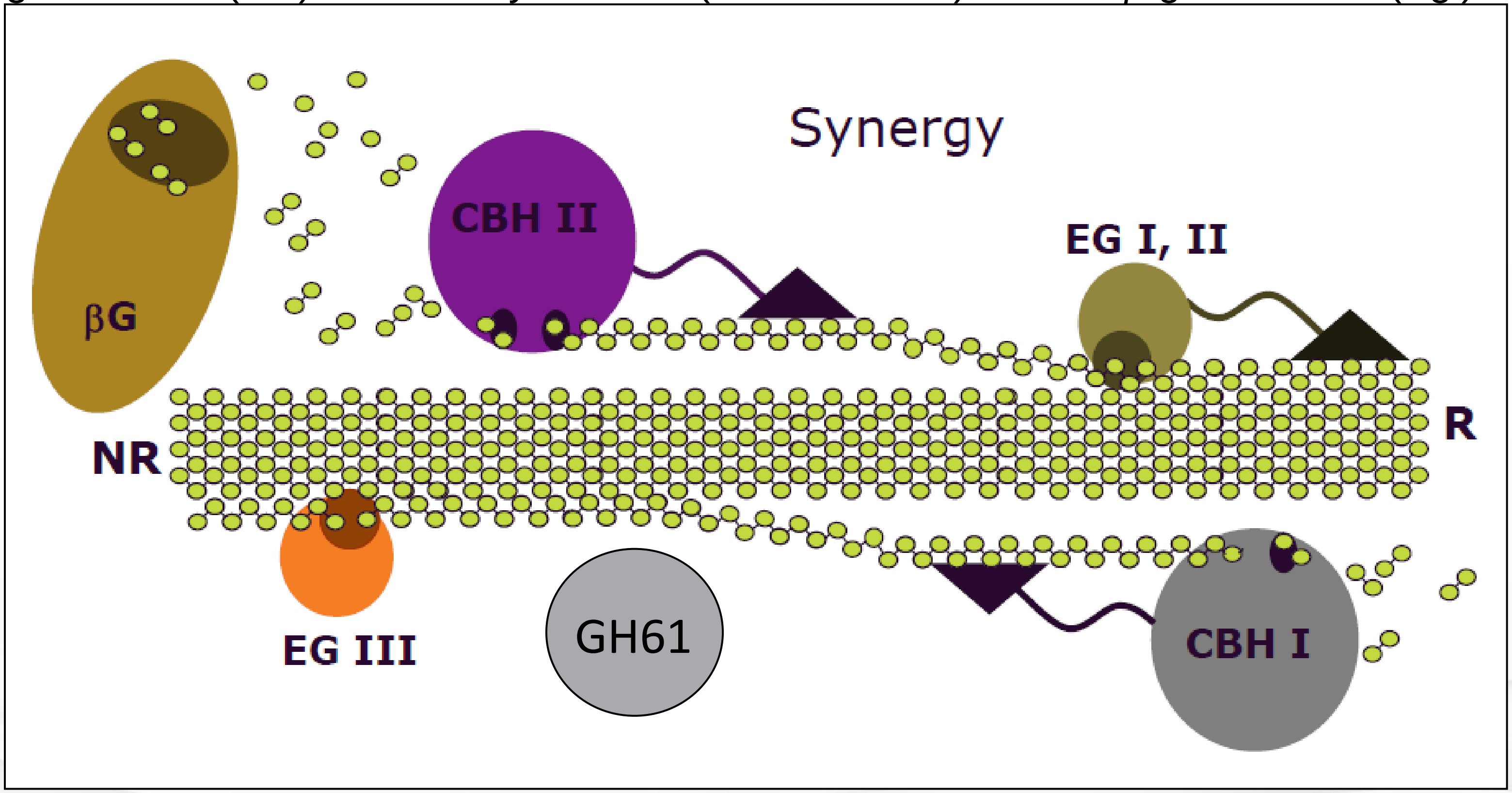
Organisms
(Sugars → Products)

Cellulose hydrolysis

A symphony of many reactions

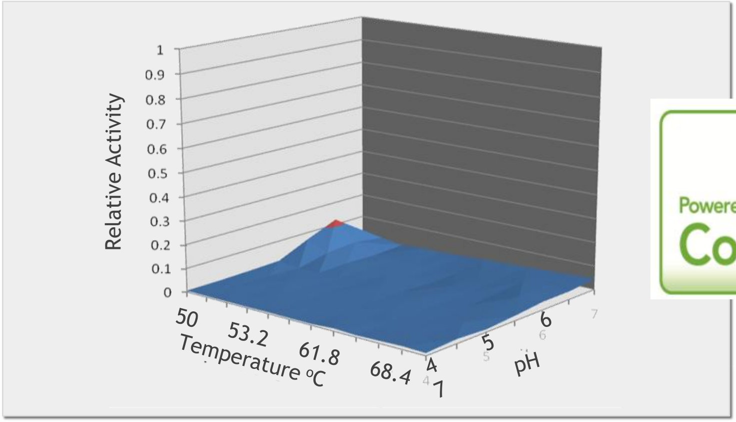
Codexis technology being used to engineer the key **enzyme types**

- Endoglucanases (EG), Cellobiohydrolases (CBH1, CBH2), GH61, β-glucosidase (Bgl)



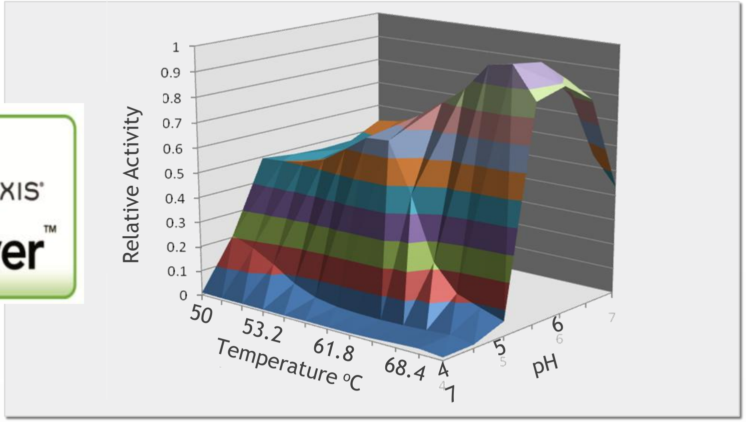
CodeXyme™ Cellulase Evolution

Wild-type Cellulase Enzyme with Limited Activity



Powered By CODEXIS CodeEvolver™

Evolved Cellulase Enzyme



Highly active cellulase enzyme package at required economics

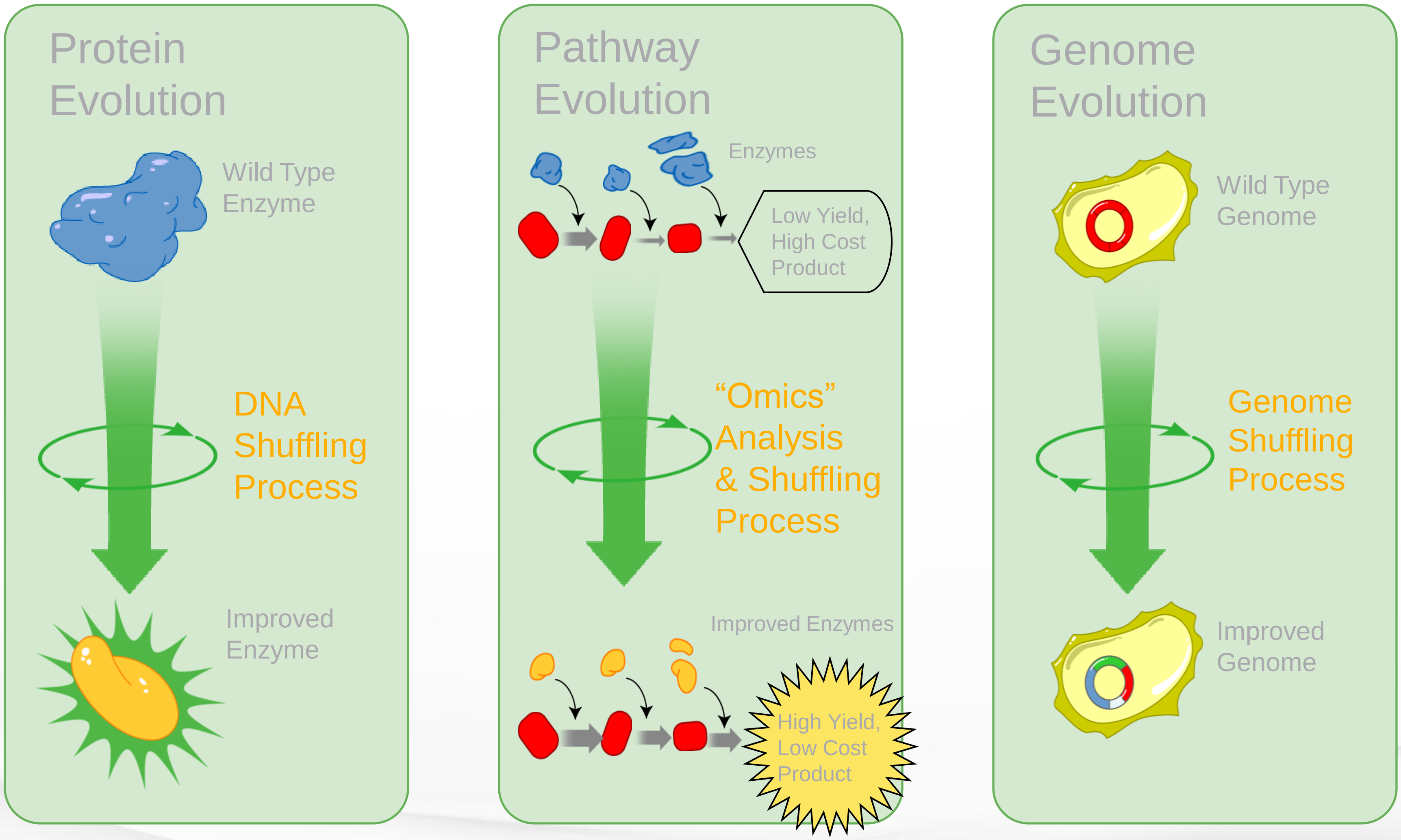
Synthetic Biology – Strains for Bio-Produced Chemicals

Synthetic Biology – Not really "plug and play"

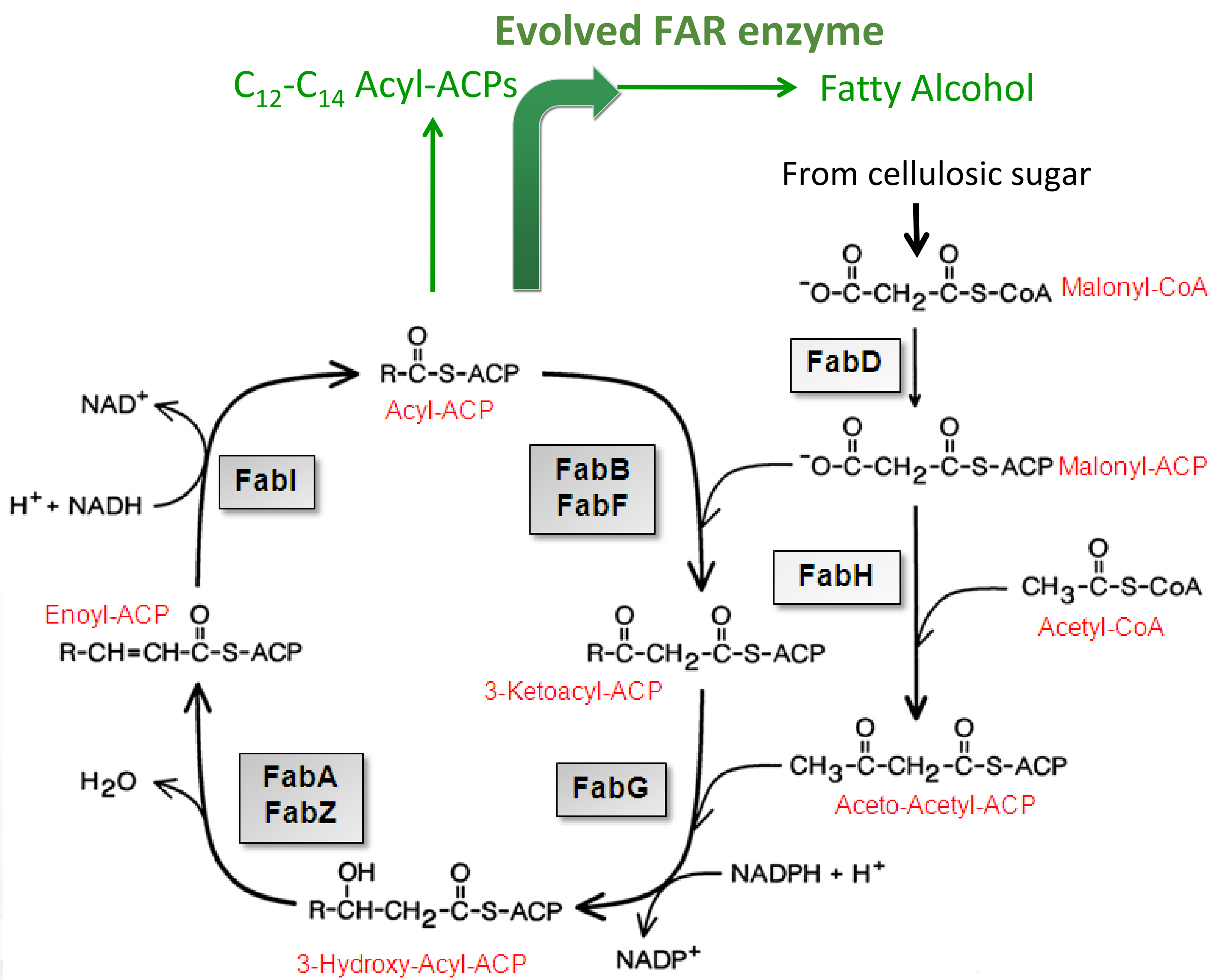
- Need unnatural enzymes for novel products
- Can't just upregulate – need evolution for kinetics, selectivity
  - Single enzyme evolution of radically different enzyme
- Need to optimize more than just route – toxicity, secretion, growth, recycle
  - Whole genome shuffling, yeast mating, and other methods for introducing, evaluating and recombining mutations all over the genome.

CODEXIS®

Strain and Enzyme Evolution Tools



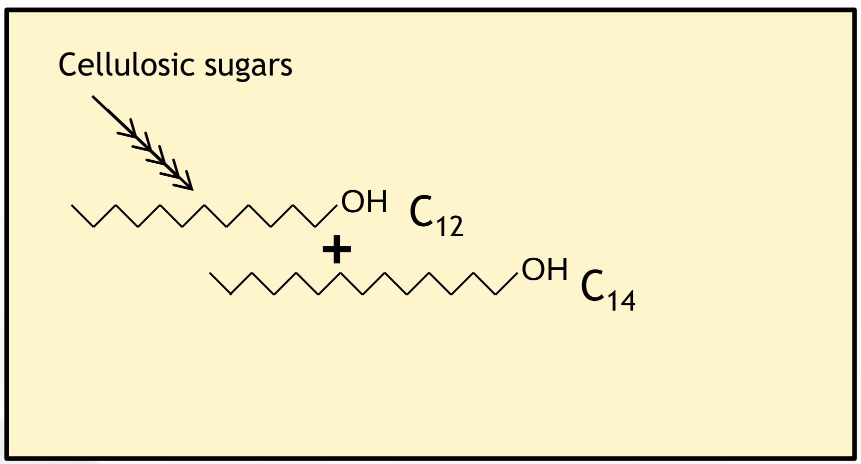
Direct C_{12}/C_{14} Alcohol from Cellulosic Sugar

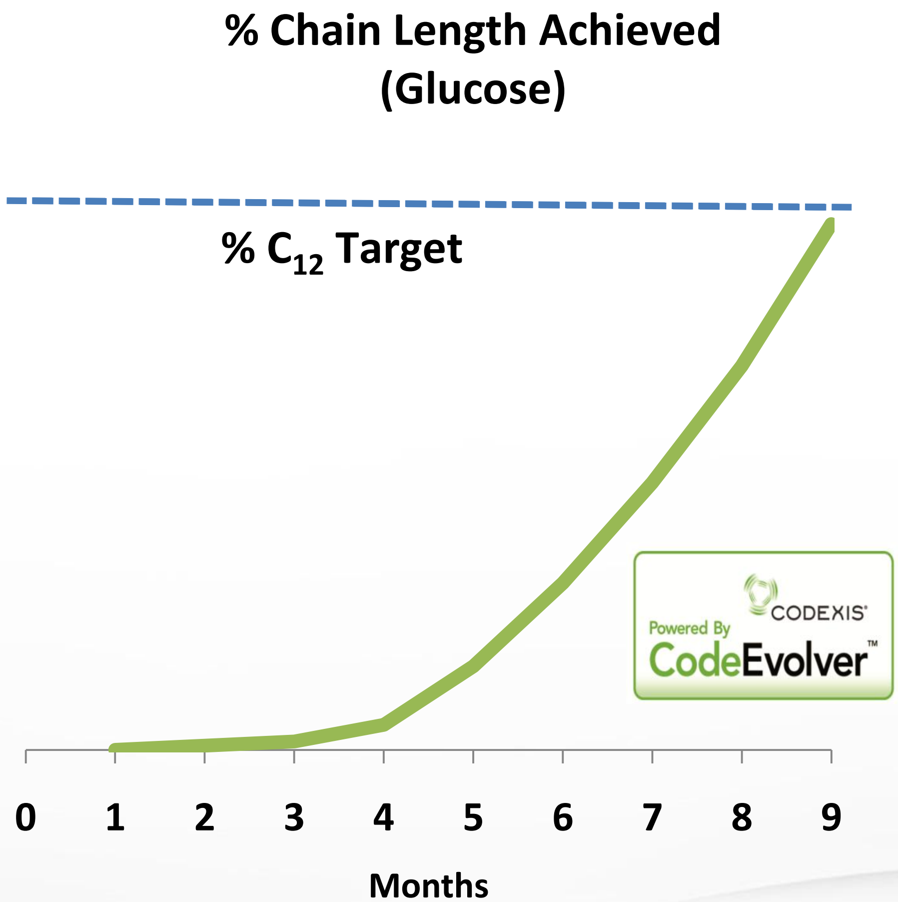


CODEXIS

Detergent Alcohol Development With CodeEvolver™

- Starting Point: C_{16}/C_{18} fatty alcohol for biobased diesel fuel
- Target: C_{12}/C_{14} fatty alcohols for biobased mid-cut detergent alcohol “drop in” applications
- Challenge: Train organism to stop at C_{12}/C_{14} instead of continuing to longer chains





CODEXIS

Codexis Approach to Bio-Produced Chemicals

Access to Low-Cost Renewable Feedstocks

- Enzyme package: Codexyme

Synthetic Biology

- Create unnatural enzymes to enable direct production of target chemical
- Use WGS to address through-put, toxicity, secretion
- Continue to develop methods for genome based ProSAR

HTP – Automation

- Process design informs assay design
- Tiered selection, PROSAR to limit screening need

Chemical Engineering

- Define recovery technologies and DSP
- Use process modeling tools to guide efforts

Acknowledgements