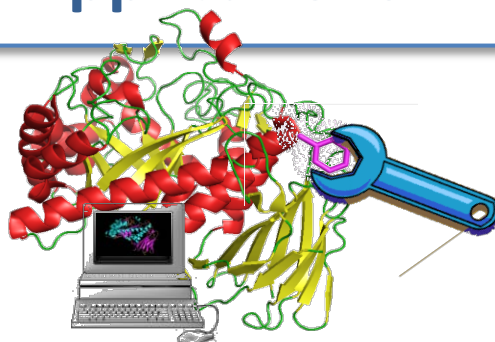


Protein Design for Therapeutic & Biotech Applications



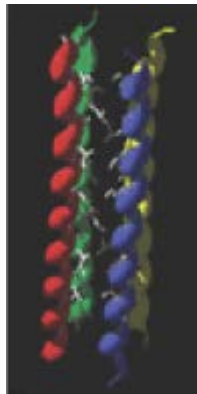
**US-EU Frontiers of Engineering Symposium
10-12 November 2014, Seattle, WA**

Session co-chairs: Isabelle André, LISBP, INSA-CNRS-INRA
Carlos J. Camacho, University of Pittsburgh

Protein design: from *in silico* models to reality

Achievements in Computational Protein Engineering: Applying practical knowledge to design

Zinc finger
structure
Dahiyat et al
(Science 1997)

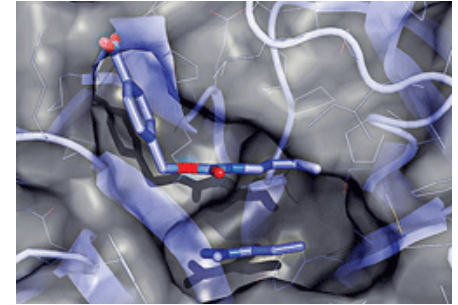


Design of
Coiled-coils
Harbury et al
(Science 1998)

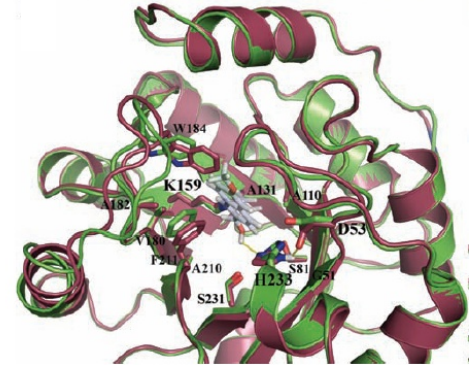


Design of
a new fold
Khulman et al
(Science 2003)

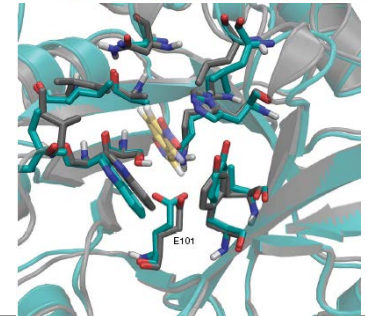
De novo design of a biocatalyst
for a stereoselective &
biomolecular reaction
(diels-alder)
Siegel et al
(Science 2010)



De novo design of an enzyme
catalyzing a multi-step reaction
(retro-aldolase)
Jiang et al
(Science 2008)



De novo design of a functional
enzyme Fonctionnelle
(Kemp elimination)
Rothlisberger et al
(Nature 2008)



1997

1998

2003
Year

2008

2010

Proteins: **Therapeutic** & Biotech applications

Red Biotechnology: Medicine

**Mechanisms
of diseases,
Targeted
medicines ...**

Protein regulation
Cell signaling
Signal transduction
Genome research
Ligand binding
Structural proteins
Enzymes
...

- Protein-based medicines
- Therapies
- Vaccines
- Recombinant proteins for treatment of chronic, severe and rare diseases
- Diagnostic tools
- ...



**Biotransformation
of lipids, carbohydrates, proteins ...**

Pulp and paper
Leather
Textile detergent
Beverage,
Animal feed
Cosmetics
...



White Biotechnology: Industry

**Biorefinery/
Green chemistry/
Sustainable processes**

**Valorization of plant materials
(cell wall, oils, carbohydrates)**

New synthons
BioPolymers
Surfactants
Lubricants
Fine chemicals
Racemic resolution



Energy

Biofuel
Ethanol
Biodiesel
Substitute of kerosene



Protein Engineering & Design strategies

- Increasing use & demand for novel proteins having requested property/function

(Semi-)rational approaches

Sequence-based &
Structure-based design of proteins &
Site-directed/saturation mutagenesis

Structural data

Computational design

Molecular modeling
Computational tools
Automated Computational Protein Design
Virtual screening
Statistical analysis

Combined approaches

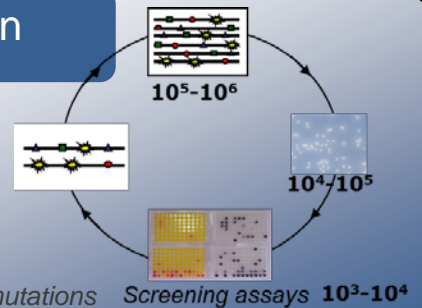
Functional Screening
from natural sources

Activity screening of
microbial collections &
metagenomics libraries
(avoiding culture)

Robotized HTS system

Directed evolution

No structural data
Random mutagenesis
Diverse library
Large library
HTS system
Accumulation of beneficial mutations



Knowledge-based design
Evolutionary methods
Computational methods
Focused libraries of mutants
Redesign & Design de novo

Stochastic approaches

Protein Design: a multi-scale challenge

2. (Re)design tunnels and channels:

*Ligand/substrate specificity
or selectivity*

*Functional Dynamics
Conformational rearrangements
Ligand transport
Tunnels
Cavities*

Jiri Damborsky, Masaryk University, Czech Republic

New concepts for rational design of enzymes

3. (Re)design Allosteric site:

Switchable function

Allosteric binding site

*Ligand/Substrate binding site
or
Catalytic reaction*

1. (Re)design Binding site:

ligand/substrate specificity or catalytic reaction

**Daniela Graß, Rötthlisberger, Arzaga, Corn
Nikolay V. Dokholyan, University of North Carolina,**
*Transformative products toward a sustainable future
Chemico-allosteric control of kinase activity in living cells*



Challenges ahead: From single proteins to networks

- Probing signaling network?
- Robustness?
- Energy efficiency?

PPI Interactome:

