Protein Design for Therapeutic & Biotech Applications

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Achievements in Computational Protein Engineering: Applying practical knowledge to design

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)

Year

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)

Protein design: from in silico models to reality
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

**White Biotechnology: Industry**
- Food, Feed, …
- Biorefinery/
  - Green chemistry/
  - Sustainable processes
- Energy
  - Biofuel
  - Ethanol
  - Biodiesel
  - Substitute of kerosene

**Biotransformation of lipids, carbohydrates, proteins …**
- Pulp and paper
- Leather
- Textile detergent
- Beverage,
  - Animal feed
  - Cosmetics
  - Racemic resolution

**Valorization of plant materials**
(cell wall, oils, carbohydrates)
- New synthons
- BioPolymers
- Surfactants
- Lubricants
- Fine chemicals
- Racemic resolution
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

Functional Screening from natural sources

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

Robotized HTS system

Computational design

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

Directed evolution

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

Combined approaches

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

Stochastic approaches

Combined approaches
Protein Design: a multi-scale challenge

1. (Re)design Binding site: ligand/substrate specificity or catalytic reaction

2. (Re)design tunnels and channels: Ligand/substrate specificity or selectivity

   Functional Dynamics
   Conformational rearrangements
   Ligand transport
   Tunnels
   Cavities

3. (Re)design Allosteric site: Switchable function

   Jiri Damborsky, Masaryk University, Czech Republic
   New concepts for rational design of enzymes

   Nikolay V. Dokholyan, University of North Carolina,
   Chemico-allosteric control of kinase activity in living cells

Daniela Grabs-Röthlisberger, Arzeda Corp
Transformative products toward a sustainable future
Challenges ahead: From single proteins to networks

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

PPI Interactome: