Structural comparison between *E. coli* and *Erwinia chrysanthemi* L-Asparaginases to facilitate rational engineering of a cancer drug

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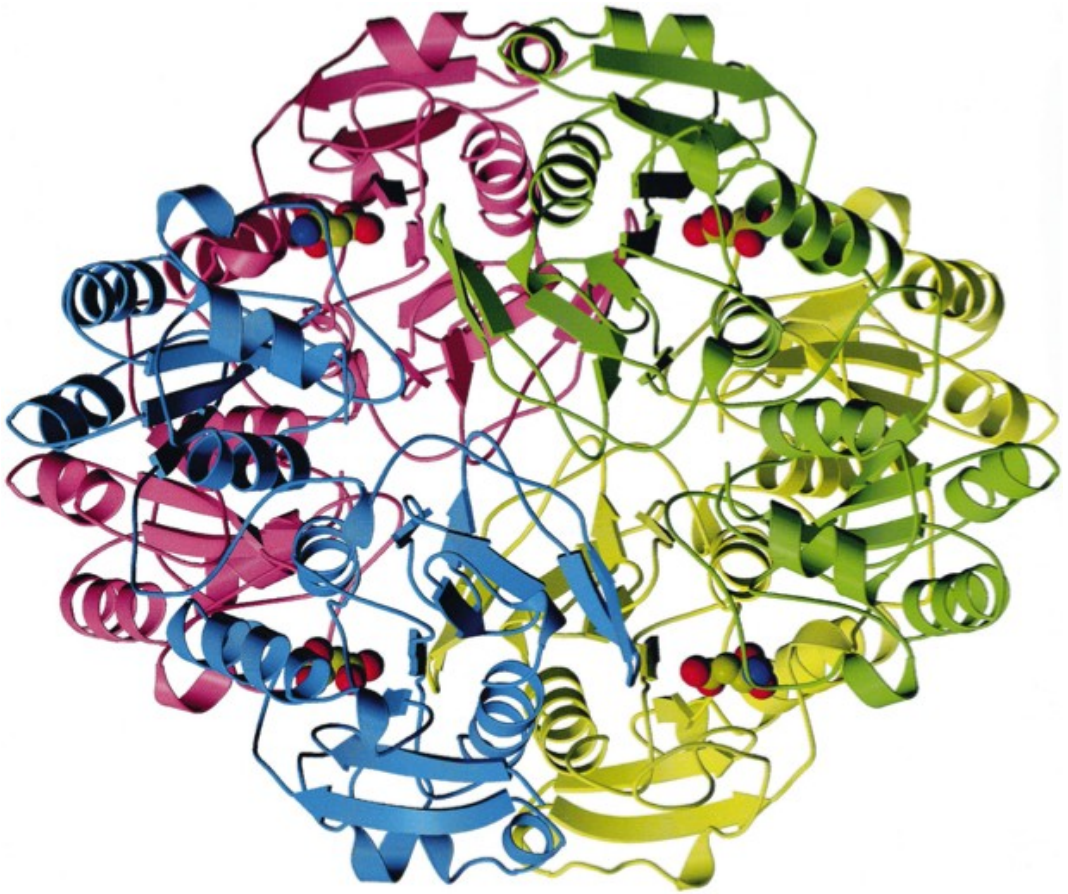
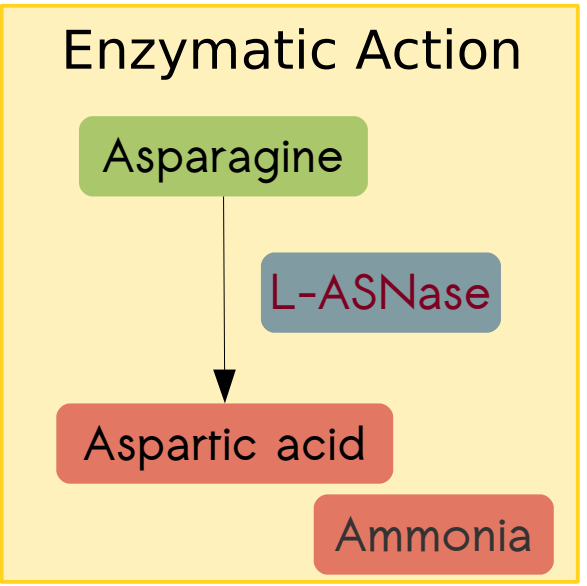
L-Asparaginase

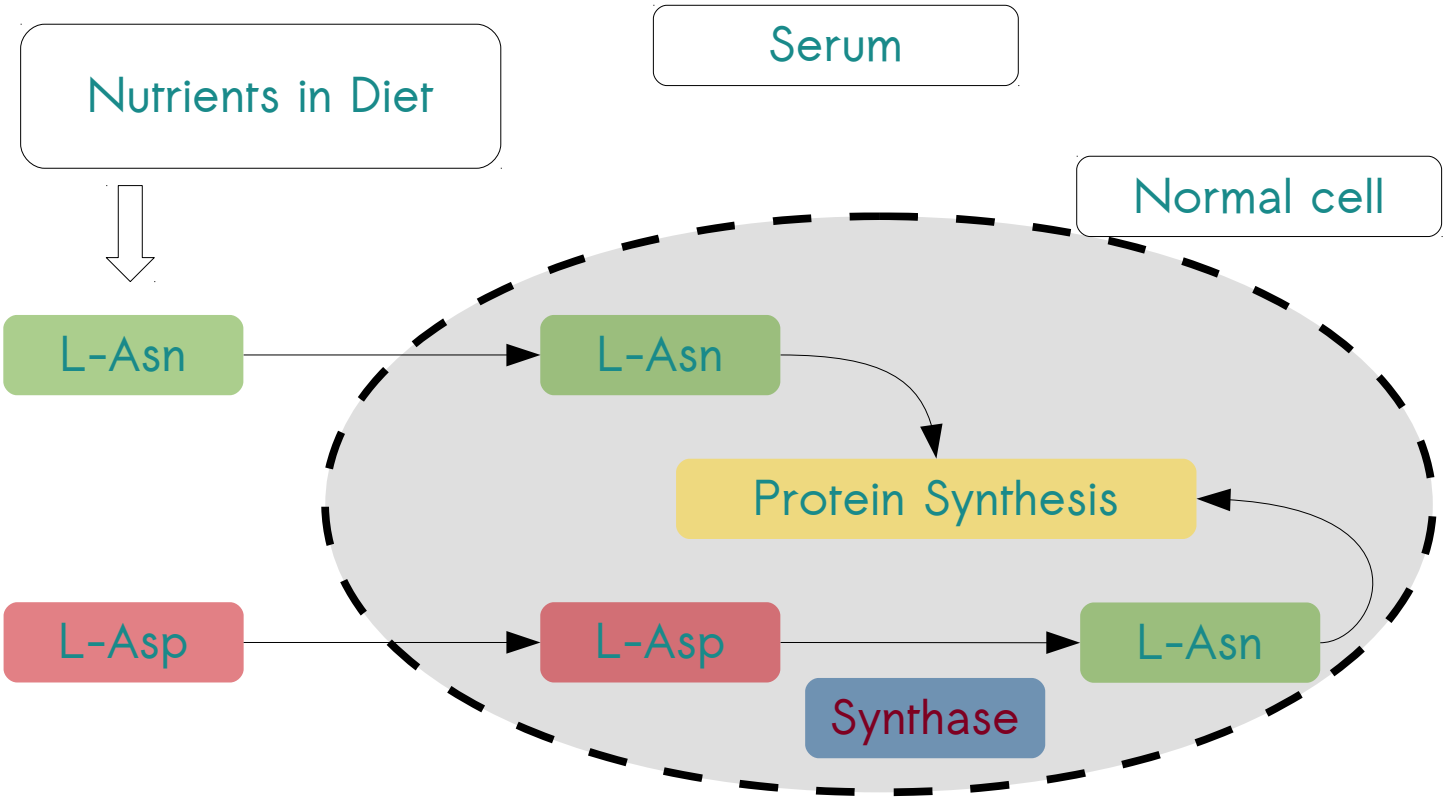


3ECA PDB structure of L-ASNase.
(Stecher, Abrahao-Neto et al., 1999)

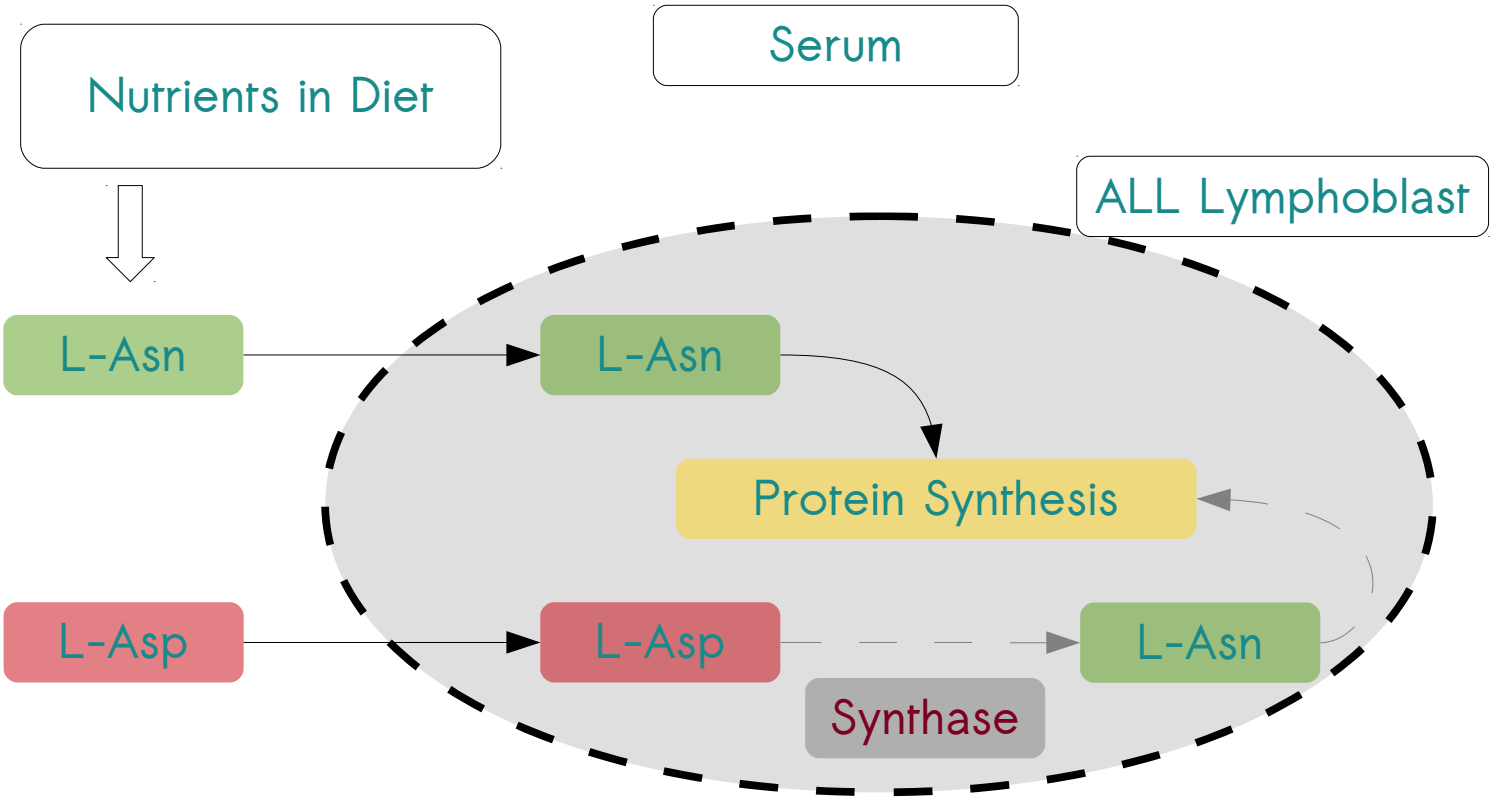


L-ASNase is used as a drug in the treatment of Acute Lymphoblastic Leukemia (ALL)

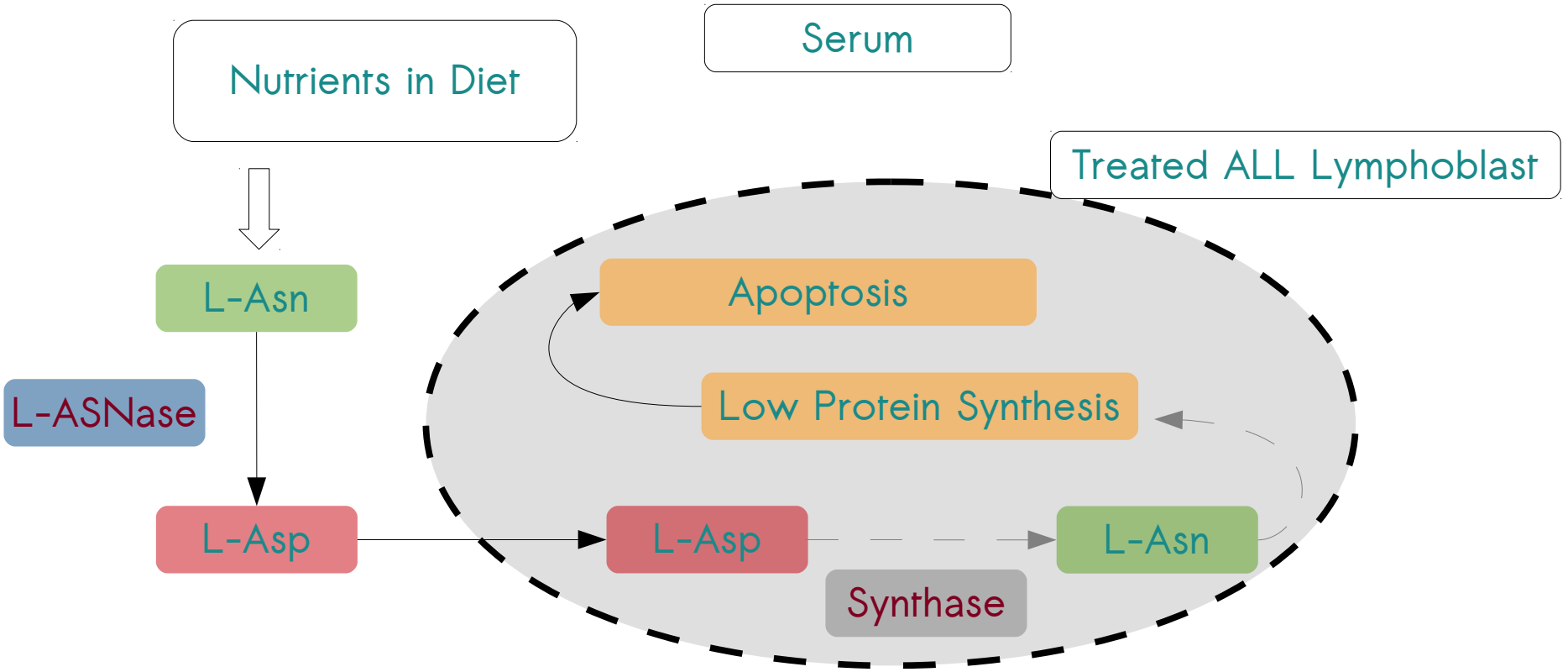
The Mechanism of Action



The Mechanism of Action



The Mechanism of Action



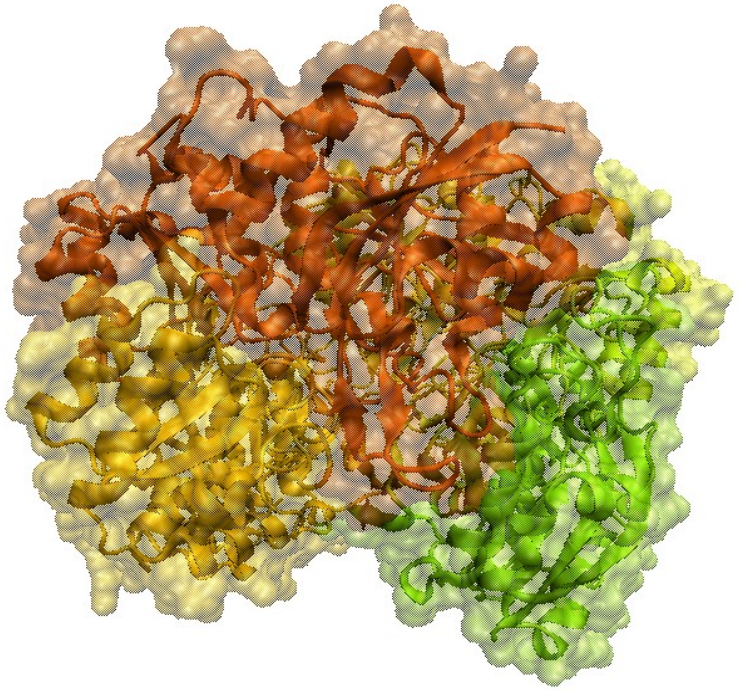
ALL Treatment

Two bacterial L-ASNases are clinically available for over 40 years.

Both present reasonable success rates and relatively mild side effects.

Eca

Escherichia coli L-Asparaginase



- First line treatment

- Prolonged half-life

(Asselin, Coppola, et al., 1993)

- Lower Glutaminase activity

(Aghaiypour, Lubkowski et al., 2001)

Era

Erwinia chrysanthemi L-Asparaginase

- Not degraded by Asparaginyl Endopeptidase

(Patel, Saha et. al., 2009)

- ~40% reduced risk of sepsis

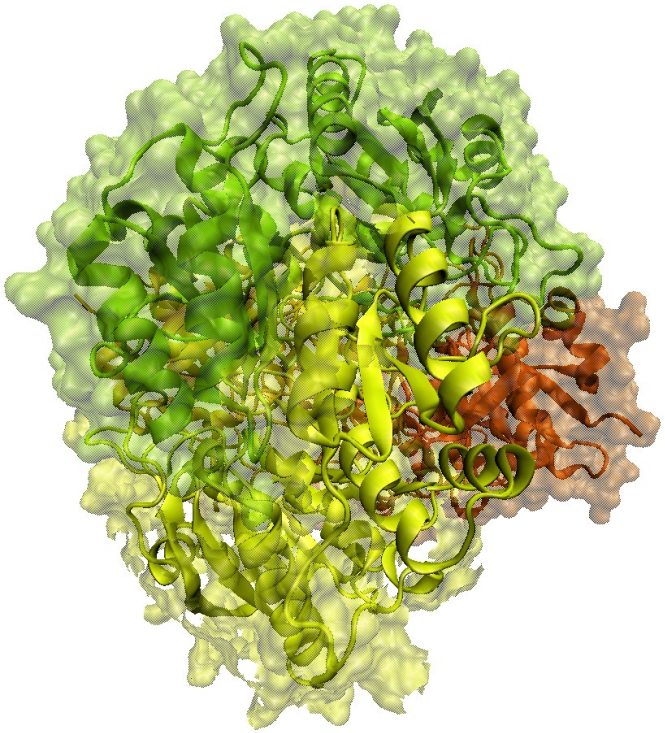
(Eden, Richards et al., 1990)

- Less neurotoxic

(Eden, Richards et al., 1990)

- Lower hypersensitivity

(Killander, Engestedt et al., 1976)



Alternative ALL Treatment

Up to 30% of the patients show allergic reactions to Eca.

(Silverman, Dalton et al., 2001)

Patients with allergic reactions to Eca can still make use of Era (no cross-reaction).

(Moola, Nicholls et al., 1994)

The Aim

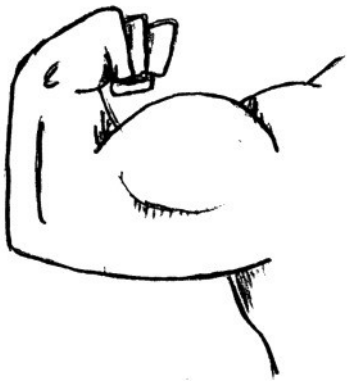
Assess similarities and differences between Eca and Era.

Engineer a protein with activity and half-life comparable to Eca that still takes advantage of lower hypersensitivity and neurotoxicity.

How to Explore Era

- Loop region and ligand binding:

  How to increase the protein activity.



- Protein stability:

  How to increase the protein half-life.

Where We Are So Far

Residues of Interest:

- Literature search
- Sequence comparison
- SNAP prediction
- Solvent accessible surface analysis
- Previous experimental results

Loop region and ligand binding:

- Molecular Dynamics protocol

Outlook and Perspectives

- Thorough comparison between Era and Eca.

- Validation of previously applied protein engineering protocol.

(Offman, Bates et al., 2011)

- Drug with lower antigenicity and similar effect.

Acknowledgments

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ISCB

ALL ROST LAB MEMBERS!

THANK YOU FOR THE ATTENTION!

Questions?