Stephanie Bath de Morais et al., J Proteomics Bioinform 2017, 10:8(Suppl)
DOI: 10.4172/0974-276X-C1-0100

The challenge of improve disease treatment with protein engineering. The contributions of X-ray crystallography

Stephanie Bath de Morais and **Tatiana A C B Souza**
FIOCRUZ, Brazil

Acute Lymphoid Leukemia is the most common neoplasia in childhood. The multi-therapeutic treatment resulted in remarkable advances in treatment of children, with 90.4% survival rate. L-asparaginase has been a central component of ALL therapy for over 40 years and acts by depleting plasma asparagine. In contrast to the normal cells, tumor cells lack the ability to synthesize asparagine and thus depend on external uptake of this amino acid for growth. Nowadays, three asparaginases are used in therapy: native L-asparaginase II from *Escherichia coli*, a pegylated form of this enzyme and L-asparaginase isolated from *Erwinia chrysanthemi*. Among the commercially available L-asparaginases, the *E. coli* enzyme presents the highest catalytic activity but also the highest toxicity, due to its further ability to hydrolyze glutamine, generating glutamate. Moreover, the immune response in patients under therapy with bacterial asparaginases can result in enzyme neutralization and the need to proceed the treatment with one of the alternative L-asparaginases. Based on the analysis of the available crystal structures we have designed, produced and crystallized E. coli asparaginase with modifications. Crystals diffracted up to 1.65 Å resolution at the Soleil Synchrotron. We combine structural analysis with kinetic and cellular approaches to identify the determinants of *E. coli* asparaginase toxicity. In addition, we have been working on the production of modified human asparaginases for structural characterization, kinetic and anti-leukemic activity assays. The introduction of human asparaginase in ALL treatment would avoid the problems caused by the bacterial enzymes, however a major difficulty in the therapeutic use of human enzyme comes from the fact that human asparaginases need to undergo activation through an auto-cleavage step, which was shown to be a low efficiency process *in vitro*, reducing the enzyme activity. These structural analyses gather insights about how engineering asparaginases can improve ALL treatment.

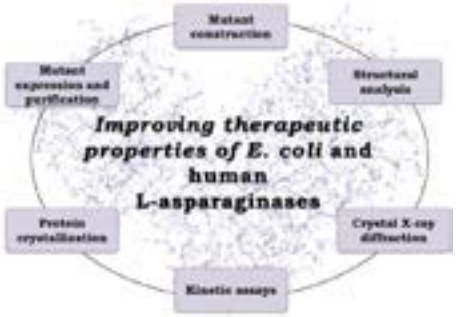

Figure1: *Schematic methodology of this project execution*

Biography

Stephanie Bath de Morais performs her PhD under Tatiana Souza supervision and coordinate projects involving advances in leukemia treatment advances. She is part of the team since 2013 and has expertise in molecular, structural and cancer biology.

stephaniebmd@hotmail.com

Notes: