INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI
SHORT ABSTRACT OF THESIS

Name of the Student	:	Ritesh Kumar
Roll Number	:	126106036
Programme of Study	:	Ph.D.

Thesis Title: "Exploring the role of methionine aminopeptidase 2 and other noncaspase proteases in programmed cell death of *Leishmania donovani*"

Name of Thesis Supervisor(s)	:	Prof. Vikash Kumar Dubey
Thesis Submitted to the Department/ Center	:	Biosciences and Bioengineering
Date of completion of Thesis Viva-Voce Exam	:	13th June 2017
Key words for description of Thesis Work	:	Programmed cell death, proteases, *Leishmania donovani*

SHORT ABSTRACT

Visceral Leishmaniasis (referred to as Kala-azar) is caused by *Leishmania donovani* which is a dimorphic protozoan parasite. The disease claims numerous lives worldwide annually. All the efforts directed to ameliorate the progression of this fatal disease have gone in vain over the years owing to drug resistance and toxicity related issues. Worldwide concerns have spurred a series of investigations by the scientific community to explore novel drug targets and to investigate the vital pathways in the parasite. Apoptotic or programmed cell death pathway of the *L. donovani* has largely remained unexplored and it promises to bring out novel insights in the drug discovery process for Leishmaniasis. In an attempt to understand the role of proteases in programmed cell death of parasite, up-regulation of mRNA transcript of various protease genes was analyzed by real time-quantitative PCR in apoptotic condition. The gene showing maximum increase in the up-regulation of mRNA transcript was considered for further studies to validate their role. The mRNA transcript of methionine aminopeptidase 2 gene (*map2*) showed maximum increase in their up-regulation in apoptotic condition. To validate the role of methionine aminopeptidase 2 (MAP2) in apoptotic processes, biochemical approach using small molecule inhibitor (TNP-470) as well genetic approach by gene knock out (*map2-/-*) was utilized. Upon inhibition of MAP2 with TNP-470, the parasite did not show apoptotic mediated cell death processes. Moreover, *map2-/-* knock out parasite shows a miltefosine less responsive phenotype. Methionine aminopeptidase 2 (MAP2) has emerged to be a key player in the apoptotic pathway of *L. donovani*. Key molecular underpinnings have been uncovered in the current work which holds significance in therapeutic interventions. Glimpses of a plethora of caspase and noncaspase proteases in the programmed cell death of the parasite have been presented in the current work.