若手研究者インターナショナル・トレーニング・プログラム(ITP)

バイオインフォマティクスとシステムズバイオロジーの国際連携教育研究プログラム 応募書類

Name: Sohiya Yotsukura

Title: Binding studies of novel phosphopeptide to BRCA1-BRCT domain

Institute: Bioinformatics Center, Institute for Chemical Research, Kyoto University

Partner institute of your choice：Theoretical Biophysics, Institute of Biology, Humboldt University

Duration of your choice: October 9, 2013 ~ January 5, 2013

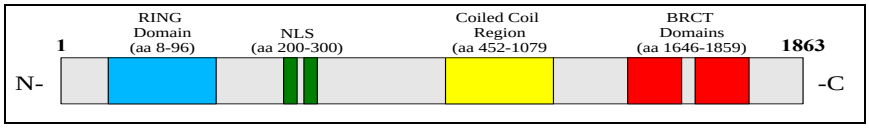
Plan：

I would like to apply for the ITP program for the three months' study in Prof. Edda Klipp's laboratory, which belongs to the Department of Theoretical Physics, Institute of Biology, Humboldt University.

Research Background and Topic:

Breast cancer occurs because of an interaction between the environment and a defective gene. Cells become cancerous as a result of genetic changes/mutations that impact cell proliferation through promoting cell division and/or inhibiting cell death. Tumour suppressor (TS) genes are the targets for many of these genetic changes. BRCA, breast cancer susceptibility gene, is a tumor suppressor gene that ensures genomic stability and helps to prevent uncontrolled cell growth through the DNA Damage Response pathway (DDR). A variety of mutations of BRCA1 are well believed to predispose mainly breast and ovarian, with some minor implications in prostate and colorectal cancer.

BRCA1 consists of four major protein domains: (i) the Zinc finger (Znf), C3HC4 type, (ii) RING domain, (iii) the BRCA1 serine domain and (iv) two BRCA1 C Terminus (BRCT) domains.



The BRCT domain is found predominantly in proteins involved in cell cycle checkpoint functions responsive to DNA damage. Structural studies in the ring domain and the BRCT domain have revealed the molecular basis by which cancer causing mutations impact the BRCA1 function. BRCT domains are 85–95 amino acid domains that comprise several distinct clusters of conserved hydrophobic amino acids that together form the core of the BRCT fold. They can be found either as single modules or as multiple tandem repeats comprising two domains, and both can occur within individual proteins in a variety of different arrangements. Possibility of binding of a novel phosphopeptide - which is lacking BRCT binding consensus (pSXXF) sequence – will be explored during this training exchange.

Plan (Continued)

The BRCT promiscuously binds to pSXXF motif containing phosphopeptides of diverse length and amino acid content. Such an observation, opens-up the possibility of new phosphopeptide binding to BRCT with a new set of binding determinants - even though it lacks the desired BRCT binding consensus sequence. The (possible) dynamical behavior BRCT and new phosphopeptide, could be theoretically explored utilizing various statistical methods and machine learning methods to find the most suitable to develop a computational predictory framework. Various methods will be tried, from simple linear correlation analysis to more complex nonlinear machine learning methods such as Bayesian networks, penalized regression and classification.

Research Objectives:

1. Mutational data was manually curated to confirm the position and the mutation type, and will be placed on a MySQL DB.
2. Histologically the breast tumors are categorized into four types: HER2+, PR+ (progesterone receptor +), ER+ (estrogen receptor +) and Triple negative. It has been postulated to be subdivided into six groups based on their protein expression level, but has yet to be correlated with its associated mutations.
3. A label propogation problem will be attempted to associate the mutations of BRCA1 with the associated phosphopeptides. The main phosphopeptides that will be individually assessed. This is because the curated data only shows mutation data with native phosphopeptide, such as Bach1 and CtIP. Since there are various experimental measurements for the interaction of the phosphopeptides with BRCA1, such as Co-IP, NMR, X-Ray, and MS, a binary label will be implemented to show interactions. For example, if a mutation inhibits binding, such as the case for position M1775 located in the base of the binding cleft, this mutations will confer an inhibition of DNA repair and therefore is a predisposition for breast tumor. Such correlation analysis,combined with classification methods will be utilized to create a brca1 phosphopeptide predictor.

In conclusion, I will not only take part in the research, but in a Computational Modeling course that will be held from November 19, 2013 ~ November 29, 2013. The course covers the basic notations of computational modeling, which focuses on approaches, model classification, and integration techniques of various NGS data. During my three months' stay in Berlin, I hope my participation and experience in the events and programs provided will allow me to develop a new perspective on my project.