## BIOGRAPHICAL SKETCH

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| NAME | POSITION TITLE |
|---|---|
| HISASHI TANAKA | Associate Professor |
| eRA COMMONS USER NAME (credential, e.g., agency login)<br>HISASHITANAKA | |

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

| INSTITUTION AND LOCATION | DEGREE *(if applicable)* | MM/YY | FIELD OF STUDY |
|---|---|---|---|
| Kyoto University | M.D. | 03/88 | Medicine |
| Kyoto University | Ph.D. | 05/97 | Surgery and Surgical Basic Sciences |
| Fred Hutchinson Cancer Research Center | PostDoctoral | 03/2006 | Cancer Genetics |

### A. Personal Statement

My career goal is to contribute to human health through scientific discoveries and innovations. During my 5-year career as a surgical oncologist, I saw many cancer patients who developed very aggressive tumors. Because none of the treatments were effective for those patients, I realized the necessity of transformational developments leading to new treatments for cancer patients.

My research focuses on the mechanism of gene amplification, a process which drives aggressive tumor phenotypes, such as tumor progression and therapy resistance. I have provided novel insights on both genetic and genomic factors involved in gene amplification (Tanaka et al., 2002, 2005, 2007 and 2009; Marotta et al., 2012b and 2013). In my search for the mechanisms of gene amplification, I have developed novel cell-based and genome-wide assays. I have also gained deep insights on human genetic variation and genome evolution (Zhao et al., 2009; Marotta et al., 2012a), subjects that are important to understand the tumor cell evolution.

More specifically, my recent research programs focus on the role of replication stress in the initiation of gene amplification. I am currently investigating the processes underlying naturally occurring stalled replication forks (Kondratova et al., in press; Watanabe et al., submitted). My program integrates knowledge from simple organisms and other model systems and test this knowledge in the setting of naturally occurring stalled forks in cancer cells. We believe that such a strategy will provide a novel insight into cancer genome instability.

In summary, armed with expertise in both the concepts (cancer biology, human genetics and molecular evolution) and methodology (molecular biology, cell biology and genomics), I am dedicated to the development of interventions for novel cancer diagnostics and treatments.

### B. Positions and Honors:

**Positions**

1988-1989 Resident in Surgery, Kyoto University Hospital, Kyoto, Japan.
1989-1993 Medical staff in Surgery, Fukui Red Cross Hospital, Fukui, Japan.
1994-1997 Graduate Student, Department of Surgical Oncology, Kyoto University Graduate School of Medicine, Japan. Research Trainee, Aichi Cancer Center Research Institute, Japan.
1998-2003 Postdoctoral Fellow, Division of Basic Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA.
2003-2006 Staff Scientist, Fred Hutchinson Cancer Research Center, Seattle, WA.
2006-2014 Assistant Professor, Department of Molecular Medicine, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland OH

Assistant Staff, Department of Molecular Genetics, Cleveland Clinic Foundation, Cleveland, OH

2014-Present Research Scientist II and Associate Professor, Department of Surgery, Cedars-Sinai Medical Center, West Hollywood CA

**Honors**

1998 Postdoctoral Fellowship of Sumitomo Life Insurance Social Welfare Foundation.
1999 Interdisciplinary Training Program, Fred Hutchinson Cancer Research Center.
2001 Interdisciplinary Training Program, Fred Hutchinson Cancer Research Center.
2002 Avon Breast Cancer Crusade Opportunity Fund (PI)
2013 Early Career Reviewer Program, Center for Scientific Review (CSR), NIH

**C. Selected Peer-Reviewed Publications:**

**5 most relevant publications**

Kondratova, A., Watanabe, T., Marotta, M., Cannon, M., Serre, D.; Segall, A., and **Tanaka, H**. (2015) Replication fork integrity and intra-S phase checkpoint suppress gene amplification. *Nucleic Acids Research* (doi: 10.1093/nar/gkv084) PMID: 25672394

Marotta, M., Chen, X., Watanabe, T., Faber. P.W., Diede, S.J., Kondratova, A., Tapscott, S.J. Tubbs, R., Stephens, R. and **Tanaka, H.** (2013) Homology-dependent end-capping as a primary step of sister chromatid fusion for the Breakage-Fusion-Bridge cycles. *Nucleic Acids Research* doi: 10.1093/nar/gkt762 PMID:23975201, PMCID:PMC3834830

Yang. H., Volfovsky, N., Rattray, A., Chen, X., **Tanaka, H.,** and Strathern, J. (2014). A method for identification of DNA palindromes. BMC Genomics 15:394 PMID:24885769, PMCID:PMC4057610

Marotta, M., Chen, X., Inoshita, A., Stephens, R., Budd, T.G., Crowe, J., Lyones, J., Kondratova, A., Tubbs, R. and **Tanaka, H**. (2012b) A common copy number breakpoint of *ERBB2* amplification in breast cancer co-localizes with a complex block of segmental duplications. *Breast Cancer Res* 14, R150. PMID:23181561, PMC4053137

**Tanaka, H.*** and Yao, M. C. (2009). Palindromic gene amplification – an evolutionary conserved role for DNA inverted repeats in the genome. *Nat. Rev. Cancer*, 9, 216-224. PMID: 19212324 (*corresponding author)

**Other selected publications**

**Tanaka, H.**, Shibagaki, I., Shimada, Y., Wagata, T., Imamura, M. and Ishizaki, K., (1996). Characterization of the p53 gene mutations in esophageal squamous cell carcinoma cell lines: Increased frequency and different spectrum of mutations from primary tumors. *Int. J. Cancer*, 65, 372-376.

**Tanaka, H.,** Shimada, Y., Imamura, M., Shibagaki, I. and Ishizaki, K. (1997). Multiple types of aberrations in the p16 (INK4a) and p15 (INK4b) genes in 30 esophageal squamous cell carcinoma cell lines. *Int. J.*
*Cancer*, 70, 437-442.

**Tanaka, H.,** Shimada, Y., Harada, H., Shinoda, M., Hatooka, S., Imamura, M. and Ishizaki, K. (1998). Methylation of the 5′ CpG island of the FHIT gene is closely associated with transcriptional inactivation in esophageal squamous cell carcinomas. *Cancer Res*., 58: 3429-3434.

Harada, H., **Tanaka, H.,** Shimada, Y., Shinoda, M., Imamura, M. and Ishizaki, K. (1999). Lymph node metastasis is associated with allelic loss on chromosome 13q12-13 in esophageal squamous cell carcinoma. *Cancer Res.* 59, 3724-9.

**Tanaka. H**., Shimada. Y., Harada. H., Shinoda. M., Hatooka. S., Imamura. M. and Ishizaki K. (2000). Polymorphic variation of the ARP gene on 3p21 in Japanese esophageal cancer patients. *Oncol Rep.* 7(3):591-3.

**Tanaka. H**., Tapscott, S.J., Trask, B.J. and Yao, M.C. (2002). Short Inverted repeats initiate gene amplification through the formation of large DNA palindrome in mammalian cells. *Proc. Natl. Acad. Sci. USA* 99, 8772-7.

**Tanaka, H**., Bergstrom, D. A., Yao, M. C. and Tapscott, S. J. (2005). Widespread and non-random distribution of DNA palindromes provides a structural platform for subsequent gene amplification. *Nat. Genet.* 37 320-7.

**Tanaka, H**.*, Cao, Y, Bergstrom, D.A., Kooperberg, C., Tapscott S. J. and Yao, M. C. (2007). Intra-strand Annealing leads to the Formation of Large DNA Palindrome and determine the Boundaries of Genomic Amplification in Human Cancer. *Mol. Cell. Biol.* 27, 1993-2002. (*corresponding author). PMCID: PMC1820508

Zhao, Y., Marotta, M., Eichler, E.E., Eng, C. and **Tanaka, H**. (2009). Linkage disequilibrium between two high-frequency deletion polymorphisms: implications for association studies involving the glutathione-S transferase (GST) genes. *PLoS Genet*. 5, e1000472. PMCID: PMC2672168

Diede, S.J., Guenthoer, J., Geng, L.N., Mahoney, S.E., Marotta, M., Olson, J.M., **Tanaka, H**., Tapscott, S.J. (2010) DNA methylation of developmental genes in pediatric medulloblastomas identified by Denaturation Analysis of Methylation Differences. *Proc. Natl. Acad. Sci. USA,* doi: 10.1073/pnas.0907606106. PMCID: PMC2806770

Guenthoer. J, Diede S.J, **Tanaka, H.**, Chai X, Hsu L, Tapscott S.J, Porter P.L. (2011). Assessment of palindromes as platforms for DNA amplification in breast cancer. *Genome Res*, PMID: 21752925

Marotta, M., Piontokivska, H., and **Tanaka, H**. (2012a) Molecular trajectories leading to the alternative fates of duplicated genes. *PLoS ONE* 7(6): e38958. PMID: 22720000, PMCID: PMC3375281

**D. Research Support:**
**Ongoing Research Support:**

R01 CA149385 (National Cancer Institute) Tanaka (PI) 07/01/2010-04/30/2015
Title*: DNA inverted repeats as an at-risk genomic motif for palindromic gene amplification*

The goal of our research is to define the initiation mechanism of gene amplification in cancer cells. Defining the initiation mechanism should provide important knowledge, as amplification of oncogenes is very often associated with advanced stages of cancer.

Administrative Supplement (2014)

Institutional Support (Cedars-Sinai Medical Center, West Hollywood, CA) 04/01/2014-03/31/2016

**Pending Support**

1 R03 CA188111-01 (National Cancer Institute) Tanaka (PI) Priority Score 28
Title: Small circular DNA as a signature of defects in DNA replication control in Cancer

1R01CA201662-01 (National Cancer Institute) Tanaka (PI)
Title: Causes and consequences of replication stress in oncogene amplification

**Trainee Awards (Current)**

American Cancer Society Post Doctoral Fellowship (To Anna Kondratova PhD)
Role: Mentor
$102,000 (07/01/2013-06/30/2015)

**Completed Research Support:**

Institutional seed grand (Cleveland Clinic Foundation) 4/1/06-6/30/10

American Cancer Society Tanaka (PI) 9/1/2008-8/31/2009
Title: *Is there a role for DNA palindrome formation in HER2 gene amplification in breast cancer?*

Ohio Research Scholar Program Tanaka (PI) 03/15/2009 – 12/14/2010
Title: *Sister Chromatid Jaxtaposition as a Determinant of Genome Stability in the Cardiovascular System.*