**Prof. Yang Wang**

**Clinical and Academic Affiliations:**
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**Education:**

- Fellowship in Skin Oncology, University of British Columbia, Canada (2008-2009)
- Doctor of Medicine, Residency in dermatology, Peking University, Beijing, China (2005-2010)
- Bachelor of Medicine, Peking University, Beijing, China (2000-2005)

**Working Experience:**

- Professor in Dermatology, Peking University First Hospital, China (2020-present)
- Associate Professor in Dermatology, Peking University First Hospital, China (2015-2020)
- Director & Principal Investigator, Skin Lymphoma Group, Peking University First Hospital, China (2012-present)
- Attending physician in Dermatology, Peking University First Hospital, China (2011-2015)

**Professional Qualifications:**

- Board of directors, International Society of Cutaneous Lymphoma (2019-present)
- Member, Society of Investigative Dermatology (2012-present)
- Member of the Youth Council, Chinese Society of Dermatology (2018-present)
- Member of Skin Pathology Council, Chinese Society of Pathology (2020-present)

**Awards and Distinctions:**

- Outstanding Young Doctor of Beijing, 2017
- Outstanding Young Dermatologists in Year 2016, Chinese Dermatologist Association, 2016
- Kligman Fellowship Award, Society for Investigative Dermatology, U.S., 2012
- Scholarship award recipient, Canadian Institutes of Health Research Skin Research Training Centre, Canada, 2008

**Research Activities / Achievements:**

My research focuses on the molecular diagnosis and pathogenesis of skin lymphoma, especially cutaneous T cell lymphoma. My research activities in recent years include:

***Establish the largest prospective skin lymphoma patient cohort in China***

I established a prospective CTCL patient cohort in Peking University First Hospital since 2010. This cohort has collected completed clinical, histological, and follow-up data for over 800 CTCL patients. It is the largest skin lymphoma patient cohort in China. Since April 2020, this cohort has been upgraded to a cloud-based nation-wide multi-center patient cohort. We have included 5 tertiary referral centers for skin lymphoma around China.

***Elucidate the molecular mechanisms underlying the large-cell transformation in cutaneous T cell lymphoma***

Large-cell transformation in CTCL is associated with poor prognosis with a 5-year survival of less than 20%. Our work identified that Paternally expressed gene 10 (*PEG10*), an imprinted gene at 7q21.3, was ectopically expressed in the large-transformed malignant T cells, which was driven by chr7q21.3 amplification. We elucidated the mechanism of PEG10 in driving large-cell transformation and discovered mechanism-based therapy for large cell transformed CTCL.

***Identify distinct cell origins of the malignant T cells in cutaneous T cell lymphoma***

By investigating the intra-lesional and inter-lesional divergence with single-cell RNA sequencing (scRNA-seq) and paired V(D)J sequencing, we proposed a model for skin lesion development in CTCL patients. Our data suggested that the temporal and spatial dynamics of skin lesion spreading is a multi-step evolutionary process, highly resembling the metastasis colonization of solid tumors. Moreover, by deciphering the intrinsic nature of malignant T cells, we identified distinct cell origins of malignant T cells in CTCL based on the transcriptome features of malignant T cells. We further elucidated that the distinct origins of malignant T cells determined distinct microenvironments in CTCL. Our findings challenged previous notions that CTCL were originated solely from skin-resident effector memory T cells and proposed a molecular subtyping scheme based on cell origin for future precision medicine in CTCL.

***Establishing molecular subtyping system based on SATB1 expression in cutaneous T cell lymphoma***

SATB1 is an essential T-cell lineage-specific chromatin organizer. Our group first reported the aberrant expression of SATB1 and its molecular functions in cutaneous T-cell lymphoma in 2011 and 2014. In the subsequent studies, we have proved that SATB1 can serve as a marker for patient prognosis and a molecular marker for disease subtyping. We showed that SATB1 defines a subtype of CTCLs with a Th2/Th17 cytokine profile with the sizeable clinical cohort. High SATB1 expression was associated with epidermal hyperplasia, eosinophil infiltration, less large-cell transformation, better treatment response to methotrexate and interferon, and a favorable prognosis in CTCL cases. We, therefore, proposed a SATB1-based molecular subtyping scheme in CTCL.

***Characterize the epigenetic aberrancies in cutaneous T cell lymphoma***

We reported that enhancer of zeste homolog 2 (EZH2), the catalytic subunit of poly- comb repressive complex 2 mediating histone H3 lysine 27 trimethylation, is overexpressed in a subset of CTCL. We demonstrated a dual role for EZH2 in promoting tumor cell survival and regulating the tumor microenvironment in CTCL. We provided a rationale for the pharmacologic inhibition of EZH2 activity in cutaneous T-cell lymphoma. Next, we report that the loss of 5-Hydroxymethylcytosine (5-hmC) is an epigenetic hallmark of CTCL. The 5-hmC level decreased with disease progression and showed a remarkable loss in the large-cell transformed CTCL samples. Pharmacological augmentation of global 5-hmC with L-ascorbic acid in CTCL cells led to remarkable 5-hmC accumulation and promoted apoptosis. Therefore, restoration of 5-hmC levels in MF may serve as a therapeutic regimen in CTCL.

***Identify the molecular markers for predicting the efficacy of HDAC inhibitors***

We identified a positive correlation between BCL11B expression and the sensitivity to HDACi in CTCL lines. BCL11B suppression in BCL11B-high cells induced cell apoptosis by de-repressing apoptotic pathways and showed synergistic effects with HDACis. Next, we identified the physical interaction and shared downstream

genes between BCL11B and HDAC1/2 in CTCL lines. This interaction was essential in the anti-apoptosis effect of BCL11B and the synergism between BCL11B suppression and HDACi treatment. Therefore, BCL11B may serve as a therapeutic target and a valuable marker for improving HDACi efficacy in advanced CTCL.

**Selected Publications:**

1. Liu F, et al, **Wang Y.** PEG10 amplification at 7q21.3 potentiates large-cell transformation in cutaneous T-cell lymphoma. *Blood*, (2021). (online ahead of print)
2. Liu X, et al, **Wang Y.** Single-cell transcriptomics links malignant T cells to the tumor immune landscape in cutaneous T cell lymphoma. *Nature Communication*, (2022) (online ahead of print)
3. Lin Y, Chen X, **Wang Y.** Generalized Asymptomatic Skin Nodules in a Young Man. JAMA Oncol 7, 628-629 (2021).
4. Zhu P, Wang Y. Multiple keratoacanthomas in a patient with myelodysplastic syndrome. *Lancet Haematol* 8, e94
(2021).
5. Gao Y, et al, **Wang Y.** Differential SATB1 Expression Reveals Heterogeneity of Cutaneous T-Cell Lymphoma. *J Invest Dermatol* 141, 607-618 e606 (2021).
6. Wen Y, Nong L, **Wang Y.** Painful Cutaneous Plaques on the Lower Legs in a Middle-aged Woman. *JAMA Oncol,* (2020).
7. Yi S, et al, **Wang Y.** Dual Role of EZH2 in Cutaneous Anaplastic Large Cell Lymphoma: Promoting Tumor Cell Survival and Regulating Tumor Microenvironment. *J Invest Dermatol* 138, 1126-1136 (2018).
8. Sun J, et al, **Wang Y.** SATB1 Defines a Subtype of Cutaneous CD30(+) Lymphoproliferative Disorders Associated with a T-Helper 17 Cytokine Profile. *J Invest Dermatol* 138, 1795-1804 (2018).
9. Qiu L, et al, **Wang Y.** Loss of 5-Hydroxymethylcytosine Is an Epigenetic Biomarker in Cutaneous T-Cell Lymphoma.
*J Invest Dermatol* 138, 2388-2397 (2018).
10. Fu W, Yi S, Qiu L, Sun J, Tu P, **Wang Y.** BCL11B-Mediated Epigenetic Repression Is a Crucial Target for Histone Deacetylase Inhibitors in Cutaneous T-Cell Lymphoma. *J Invest Dermatol* 137, 1523-1532 (2017).
11. **Wang Y,** et al. SATB1 overexpression promotes malignant T-cell proliferation in cutaneous CD30+ lymphoproliferative disease by repressing p21. *Blood* 123, 3452-3461 (2014).
12. **Wang Y,** et al. Deficiency of SATB1 expression in Sezary cells causes apoptosis resistance by regulating FasL/CD95L transcription. *Blood* 117, 3826-3835 (2011).