



Helicobacter pylori Biology and Cancer Metabolism

Prof. Wen-Ching Wang (王雯靜), Institute of Molecular and Cellular Biology

Helicobacter pylori Biology

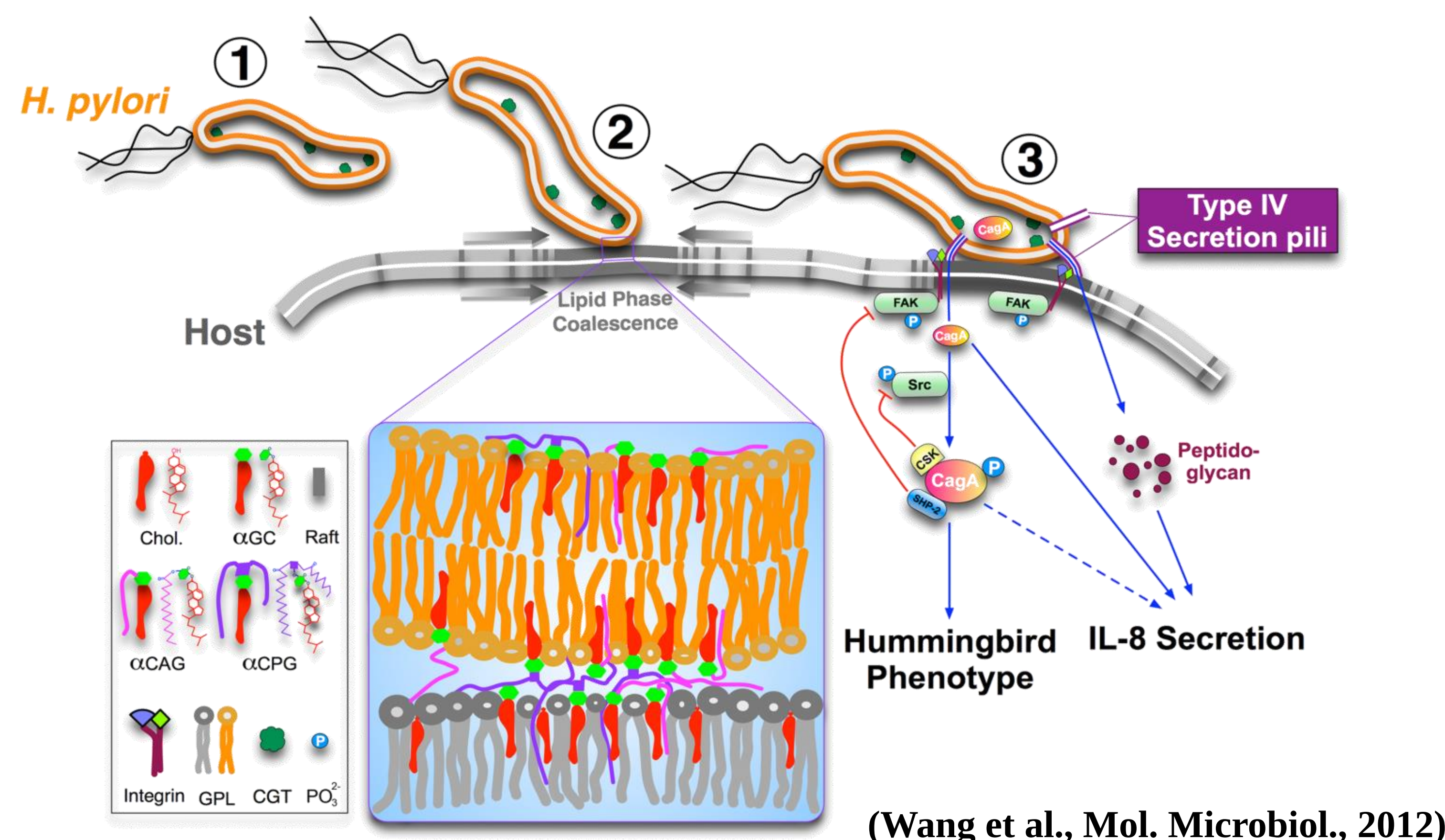


Figure 1. A proposed model of accumulated cholesteryl glucosides (CGs) in the membranes leads to the raft phase coalescence that triggers the formation of the TFSS pilus. CGs that are synthesized by membrane-bound cholesterol-α-glucosyltransferase (CGT) are associated with the bacterial membranes in the absence of host contact (step 1; ①). Upon attachment with the host membranes (step 2; ②), cholesterol is extracted from the host cells for glucosylation by bacterial CGT. In parallel, the fluctuating CGs in bacteria may drift into the lipid bilayer of the plasma membrane (magnified illustration). Accumulated cholesterol and CGs facilitate the selective lateral-phase segregation and induce the membrane assemblage and raft coalescence on the host-bacterium contact sites, which may serve as a signal to trigger the formation of the TFSS pilus. The mature TFSS subsequently delivers the effectors, CagA and peptidoglycan, into the host cytoplasm (step 3; ③). After translocation, CagA is tyrosine phosphorylated by Src family kinases and triggers downstream signaling events leading to cytoskeletal rearrangement and hummingbird phenotype. The injected peptidoglycan induces the production of pro-inflammatory cytokine interleukin-8 (IL-8). CGs include cholesterol-α-D-glucopyranoside (aCG), cholesteryl-6'-O-tetradecanoyl-α-D-glucopyranoside (aCAG), cholesteryl-6'-O-phosphatidyl-α-D-glucopyranoside (aCGP). Chol, cholesterol; GPL, glycerophospholipid; CGT, cholesterol-α-glucosyltransferase; Csk, C-terminal Src kinase; SHP-2, SH2 domain-containing tyrosine phosphatase-2

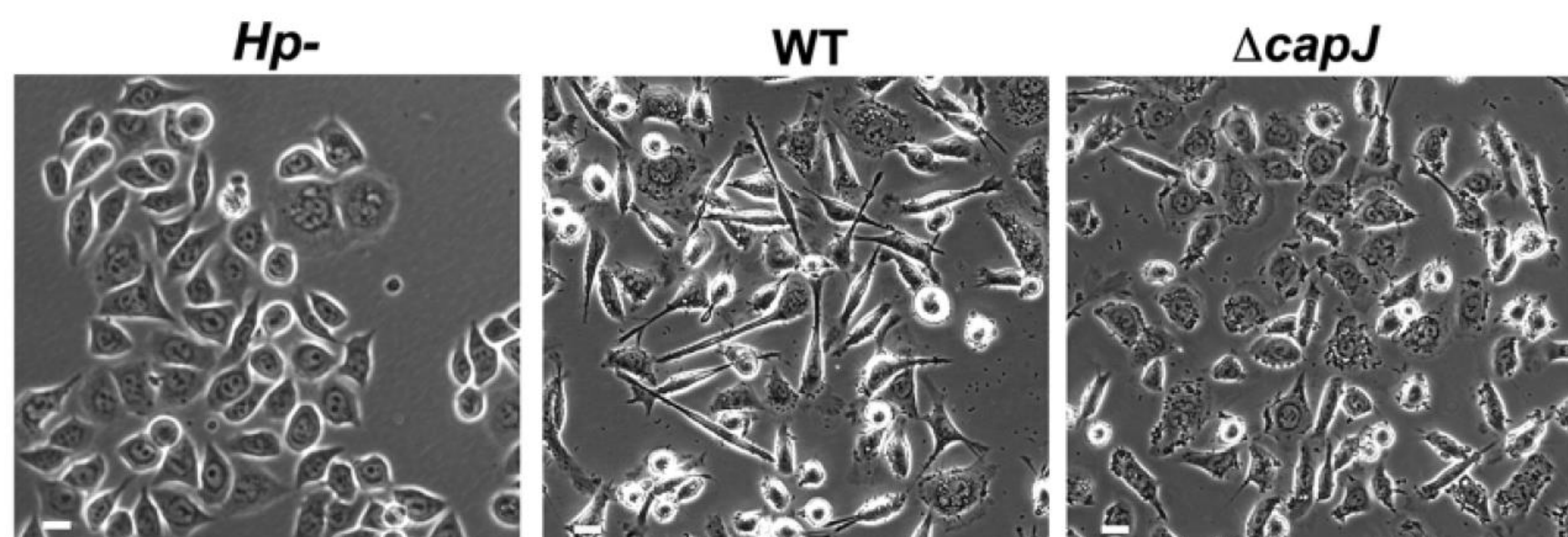


Figure 2. 26695-Δ*capJ* *H. pylori* has significantly reduced ability to form hummingbird cells as compared to wild type. AGS cells were either not infected (Hp-) or infected with strain 26695 (WT) or 26695-Δ*capJ* (Δ*capJ*) at an moi of 50 for 3 h. Cells were visualized by phase-contrast microscopy to assess AGS cell morphology.

Structure-based Screening of Antibacterial Agents

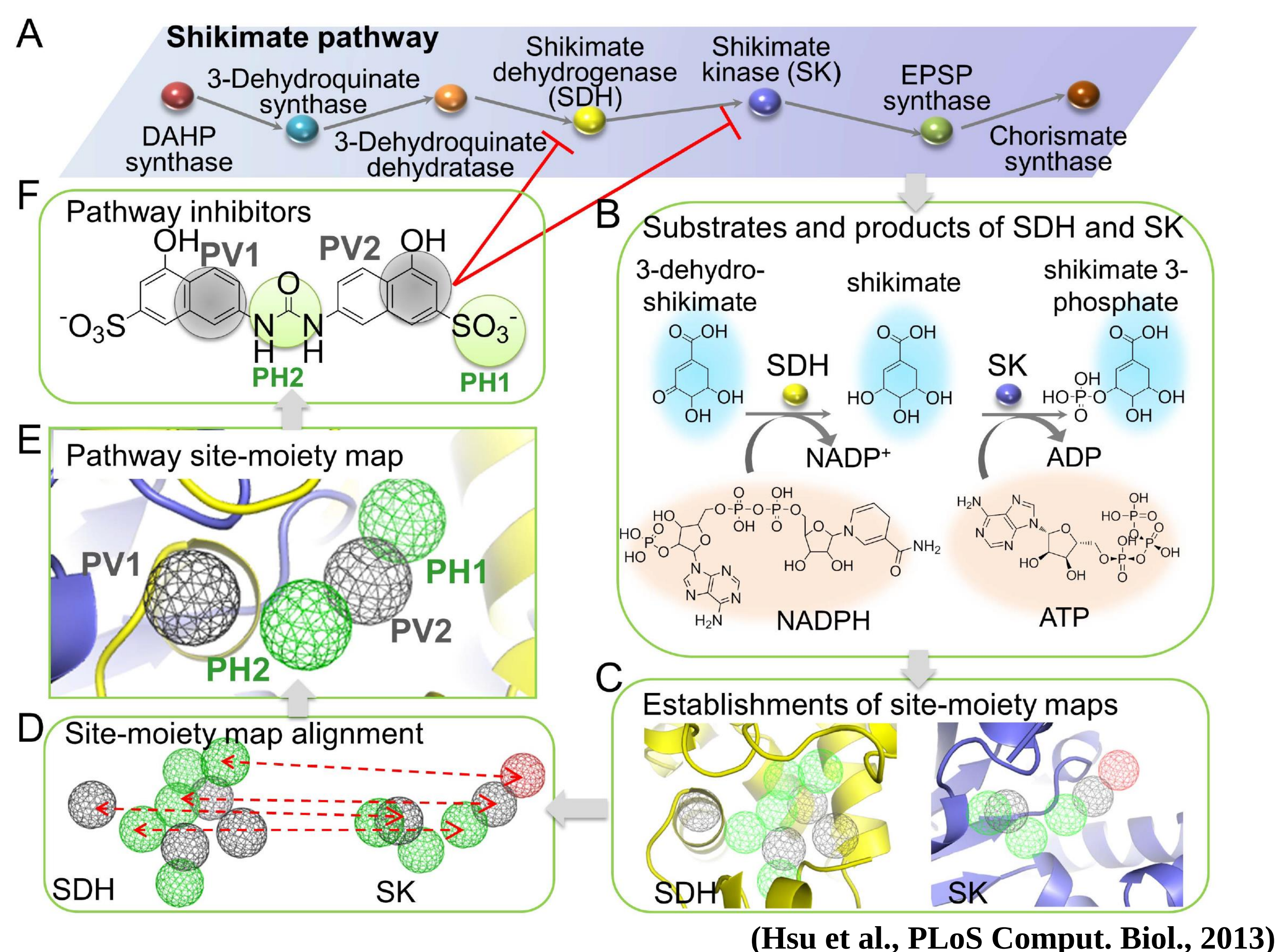


Figure 3. Overview of pathway-based screening strategy for identifying conserved binding environments and multitarget inhibitors of multiple proteins. (A) The proteins in the shikimate pathway. (B) Chemical reactions of shikimate dehydrogenase (SDH) and shikimate kinase (SK). SDH converts 3-dehydroshikimate into shikimate using NADPH and then SK converts shikimate into shikimate 3-phosphate by ATP. These three compounds share the same substructure (blue region). (C) Establishment of site-moiety maps of SDH and SK. A site-moiety map represents the binding environments of a protein binding site by anchors. (D) The site-moiety map alignment of SDH and SK for identifying the conserved binding environments (pathway anchors). (E) Pathway anchors of SDH and SK. Hydrogen-bonding and van der Waals anchors are colored in green and gray, respectively. (F) Pathway inhibitors identified by the pathway anchors.

Cancer Metabolism

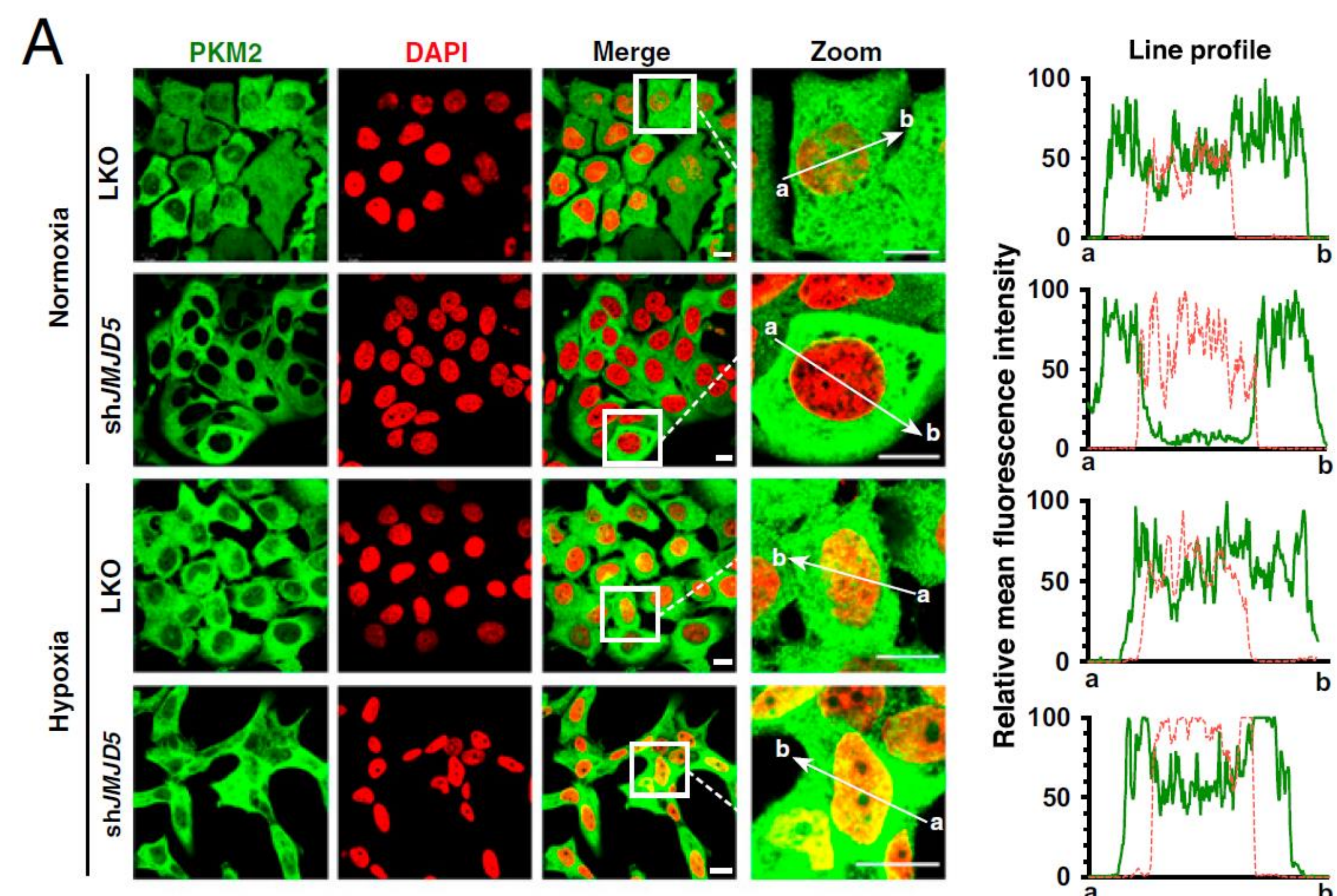


Figure 4. JMJD5 regulates the nuclear translocation of PKM2. (A) Subcellular localization of PKM2 in MCF-7 cells. Cells were immunostained with anti-PKM2 (PKM2, green). The nucleus is marked with DAPI (red). Merged images (Merge) are shown. The framed regions are zoomed in the fourth row (Zoom). The line profiles of PKM2 and DAPI signals were measured by ZEN 2011 (Carl Zeiss) software. (Scale bars, 10 μm.)

(Wang et al., PNAS, 2014)

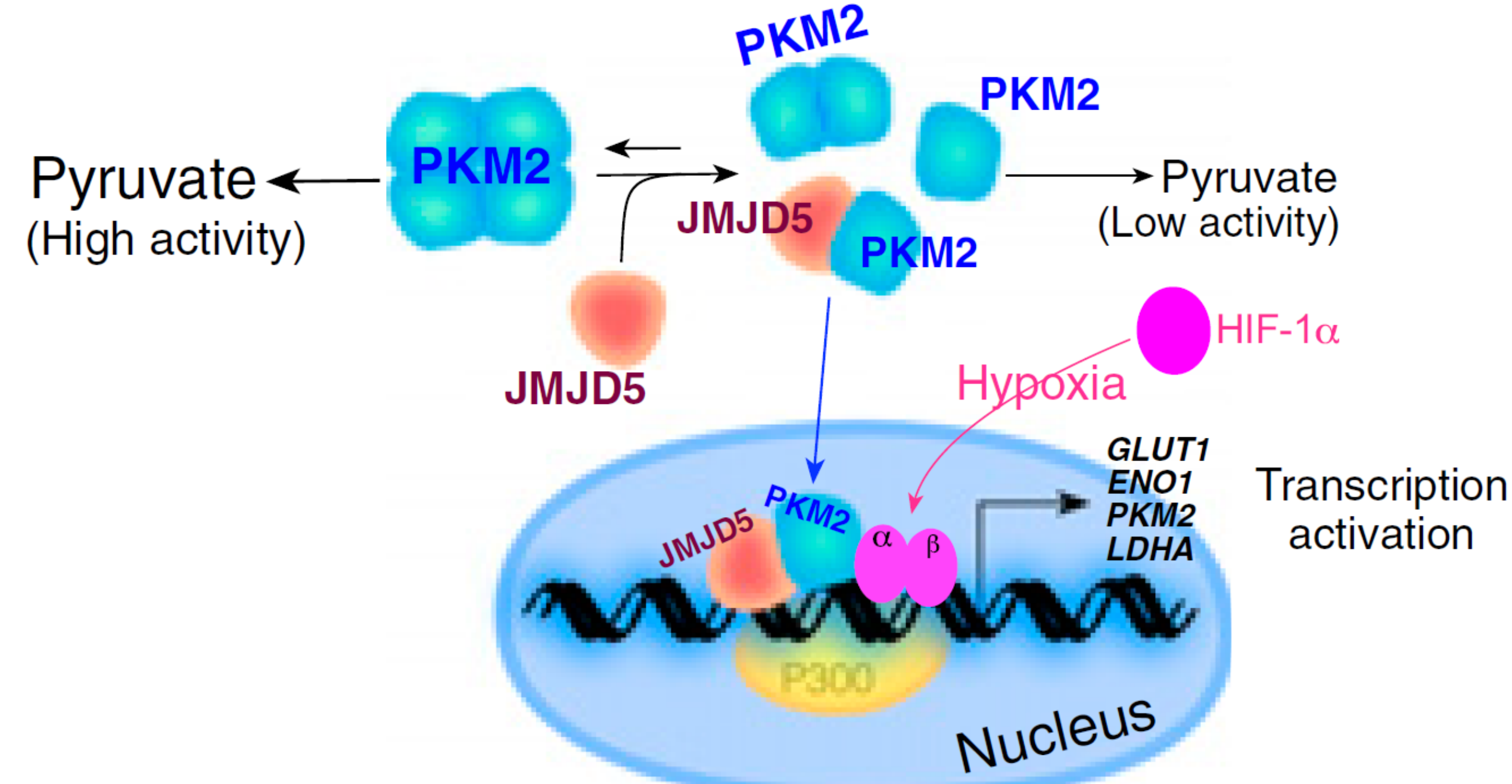
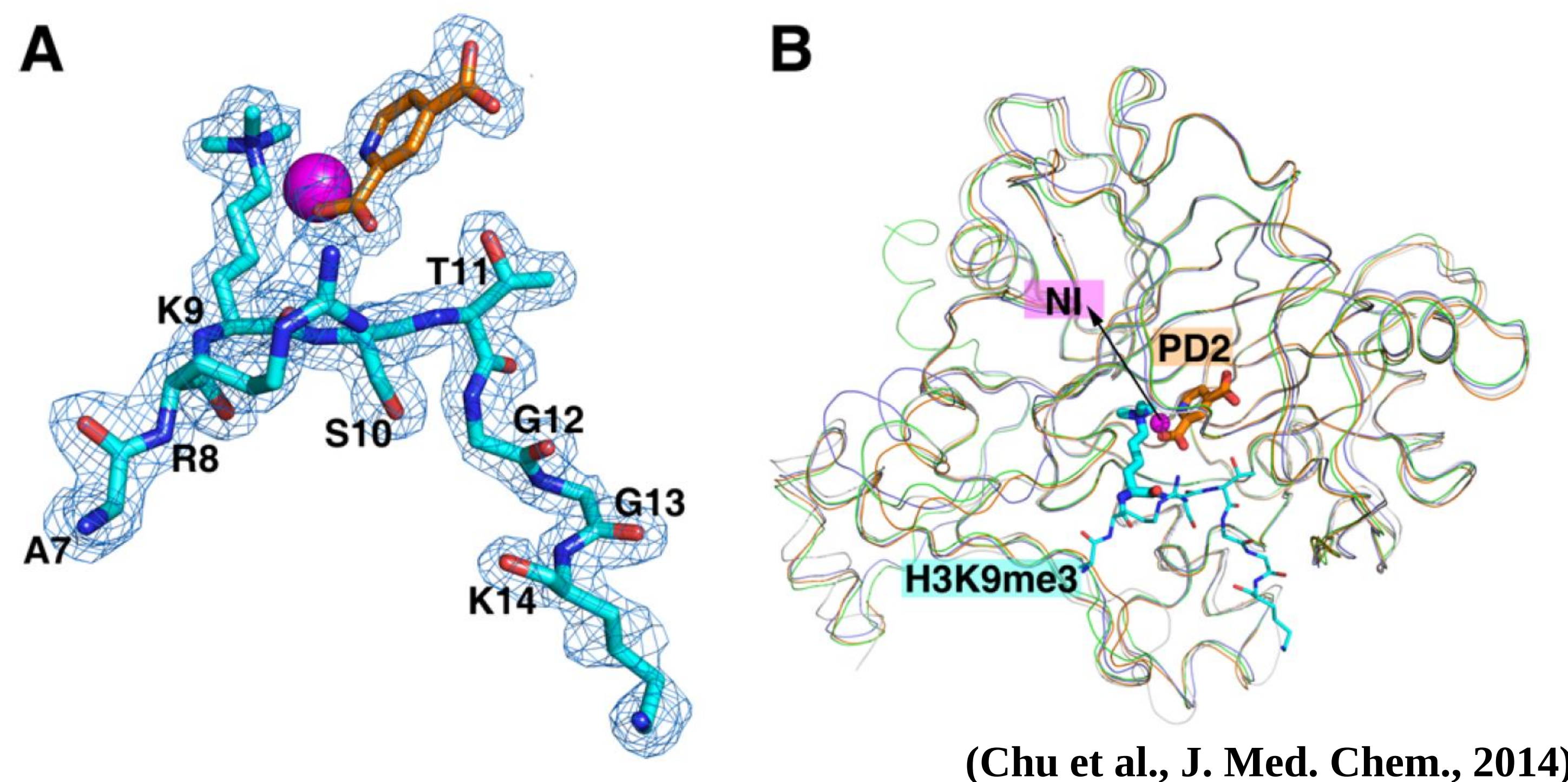


Figure 5. The proposed model that depicts JMJD5 as a major regulator in PKM2-stimulated HIF-1α metabolic reprogramming. JMJD5 and PKM2 are corecruited to HREs of LDHA and thereby specifically enhance HIF-1α binding.

Design of Epigenetic Drugs



(Chu et al., J. Med. Chem., 2014)

Figure 6. KDM4B·2·H3K9me3 crystal structure. (A) Electron density map for Ni(II), 2, and H3K9me3 peptide. The 2Fo - Fc electron density maps are contoured at 1.0σ. (B) KDM4A (PDB code: 2OQ6), KDM4B (this study; PDB code: 4LXL), KDM4C (PDB code: 2XML), and KDM4D (PDB code: 4HON) are colored green, orange, blue, and gray, respectively. The stick models of compound 2 (pyridine, 2,4- dicarboxylic acid) and the peptide are colored orange and cyan, respectively. Oxygen, nitrogen, and nickel atoms are colored red, blue, and magenta, respectively.



We welcome new members who are interested in *H. pylori* pathogenicity, cancer metabolism, epigenetics, and structural biology!