Phylogeny  
• Orthologous proteins are reported in Bos taurus (73 % identity), Mus musculus, Xenopus laevis and Macaca mulatta, indicating broad vertebrate conservation (hanna2020developmentofwee2 pages 7-8, nozawa2023oocytespecificwee1likeprotein pages 1-2, han2006newpathwaysfrom pages 1-2, nozawa2023oocytespecificwee1likeprotein pages 12-13).  
• WEE2 belongs to the WEE kinase family within the CMGC group of the human kinome, together with WEE1 and PKMYT1 (hanna2020developmentofwee2 pages 5-6).  
• The WEE2 and WEE1 catalytic domains are nearly identical except for a D386A substitution in the solvent-exposed specificity pocket (hanna2020developmentofwee2 pages 5-5).

Reaction Catalyzed  
• ATP + CDK1(Tyr15) → ADP + CDK1(pTyr15) (hanna2020developmentofwee2 pages 2-3).

Cofactor Requirements  
• Specific divalent-cation dependence has not been reported for human WEE2 in the available enzymatic studies (hanna2020developmentofwee2 pages 2-3).

Substrate Specificity  
• Proven physiological substrate: CDK1 phosphorylated on Tyr15 (hanna2020developmentofwee2 pages 2-3).  
• The 2024 tyrosine-kinome atlas clusters WEE2 among dual-specificity kinases but does not define a unique consensus peptide motif (yaronbarir2024theintrinsicsubstrate pages 2-3).

Structure  
• The protein comprises an N-terminal regulatory segment followed by a canonical bilobal kinase domain characteristic of WEE family members (hanna2020developmentofwee2 pages 5-5).  
• Crystal analysis shows a closed P-loop conformation and the unique D386A residue in the specificity pocket, distinguishing WEE2 from WEE1 (hanna2020developmentofwee2 pages 5-5).  
• An extended acidic loop preceding the DLG motif and a single PEST degradation site further differentiate WEE2 from WEE1 and PKMYT1 (hanna2020developmentofwee2 pages 5-6).  
• Crystal structures reveal conserved VAIK, HRD and DFG motifs forming the catalytic core and supporting canonical kinase architecture (hanna2020developmentofwee2 pages 5-5).

Regulation  
• PKA-dependent phosphorylation during prophase I augments WEE2 activity to sustain germinal-vesicle arrest (han2006newpathwaysfrom pages 2-3).  
• Fertilization-induced Ca²⁺ oscillations activate CaMKII, which phosphorylates WEE2 to inactivate MPF and allow metaphase II exit (nozawa2023oocytespecificwee1likeprotein pages 1-2).  
• CDK1 and Polo-like kinase phosphorylations promote WEE2 down-regulation followed by SCF-mediated ubiquitination (han2006newpathwaysfrom pages 2-3).  
• During prophase I WEE2 is sequestered in the germinal vesicle and redistributes when meiosis resumes (hanna2020developmentofwee2 pages 3-4).  
• Small-molecule binding to an allosteric pocket stabilizes an inactive conformation of full-length WEE2 (hanna2020developmentofwee2 pages 5-6).

Function  
• Expression is restricted to oocytes and zygotes with negligible somatic expression (hanna2020developmentofwee2 pages 1-2).  
• WEE2 phosphorylates CDK1 Tyr15 to keep MPF inactive and maintain germinal-vesicle arrest during dictyate prophase I (hanna2020developmentofwee2 pages 2-3).  
• CDC25B antagonizes WEE2 after the LH surge to permit meiosis I entry, whereas CaMKII-reactivated WEE2 at fertilization ensures pronuclear formation (hanna2020developmentofwee2 pages 3-4).  
• Upstream regulators include PKA, CaMKII, CDK1 and Polo-like kinase; the primary downstream effector is the CDK1/cyclin B complex (han2006newpathwaysfrom pages 2-3).  
• Functional redundancy with WEE1 and MYT1 mitigates the impact of Wee2 deletion on mouse fertility (nozawa2023oocytespecificwee1likeprotein pages 6-8).

Inhibitors  
• MK-1775 (Adavosertib) is a type I ATP-competitive inhibitor that blocks both WEE2 and WEE1 activity (hanna2020developmentofwee2 pages 8-9).  
• GPHR-00336382 binds an allosteric pocket on full-length WEE2 with low-micromolar IC₅₀ (hanna2020developmentofwee2 pages 1-2).  
• GPHR-00355672 targets the isolated kinase domain, exhibiting selective inhibition at low-micromolar potency (hanna2020developmentofwee2 pages 6-7).

Other Comments  
• Loss-of-function variants such as p.Asp380Leufs*, p.Arg200Ter and p.His337Tyrfs* cause total fertilization failure in women while leaving menstrual cycles intact (hanna2020developmentofwee2 pages 4-5).  
• Wee2-null female mice show normal ovulation yet a modest reduction in litter size, underscoring species-specific redundancy (nozawa2023oocytespecificwee1likeprotein pages 6-8).  
• Selective pharmacologic inhibition of WEE2 is being explored as a non-hormonal female contraceptive strategy with limited somatic toxicity (hanna2020developmentofwee2 pages 8-9).

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