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**Unlocking the Secrets of Vitamin D-Dependent Gene Regulation: Molecular Structures of Rat VDR-Ligand-Coactivator Complexes.** Janeen L. Vanhooke<sup>1</sup>, Matthew M. Benning<sup>2</sup>, Cary B. Bauer<sup>2</sup>, J. Wesley Pike<sup>1</sup>, Hector F. DeLuca<sup>1</sup>, <sup>1</sup>Univ. of Wisconsin-Madison, Dept. of Biochemistry, <sup>2</sup>Bruker-AXS Inc., Madison, WI USA.

The vitamin D receptor (VDR) mediates the actions of the hormone  $1\alpha,25$ -dihydroxyvitamin  $D_3$  through its function in the nucleus as a transcriptional regulator. Hormone binding promotes association of the VDR and RXR (retinoid X receptor) on specific promoter elements in target genes and facilitates recruitment of coactivator proteins that are also involved in transcriptional control. The coactivator DRIP205 and coactivators of the SRC family bind in a hydrophobic groove of the ligand-bound VDR via a consensus LXXLL sequence. We have determined the molecular structure of the rat VDR complexed with a peptide containing the LXXLL sequence of DRIP205 and several 2-substituted vitamin  $D_3$  analogs of varying biological activity. The complexes are virtually identical; superposition of the analog-containing structures on that with the natural hormone yields rms deviations of approximately 0.2 Å, which are roughly equivalent to the estimated coordinate errors. It is likely that very small structural changes influence the activity of the analogs. We are presently performing an objective comparison of the structures using an error-scaled difference distance matrix method.