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MEETING ABSTRACT

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Characterising the 'hold-and-pull' mechanism of the creatine transporter (CRT1) occlusion through an *in silico* approach

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Background: In the human body, energy buffering during periods of high ATP consumption is in part achieved through the creatine–phosphocreatine system, which requires creatine to be uptaken from the blood by the membrane-embedded creatine transporter (CRT1). Malfunction of CRT1 is associated with creatine transporter deficiency, for which there is only limited treatment. However, thus far no empirically-solved structure of CRT1 has emerged, impairing our understanding of the structure–function relationship of this protein.
Methods: Here we use a homology modelling approach to generate a theoretical structure of CRT1, and confirm our predictions through experimental validation.
Results: We show that a key residue at the substrate binding site, C144, is not present in a charged state, contrary to previous proposals. We then dock creatine into the substrate binding site, and show that the mechanism of CRT1 occlusion follows the 'hold-and-pull' mechanism of the serotonin transporter, with a key interaction chain of Y148–creatine–Na^+ essential to the process of occlusion.
Discussion: To the best of our knowledge, our study represents the first set of molecular dynamics simulations aimed at exploring the structure–function relationship of CRT1. Given the clinical importance of CRT1, our insights could provide an important launching pad for further studies aimed at developing CRT1 ligands.
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Keywords: molecular dynamics simulations – creatine transporter – CRT1 – protonation

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