Cell Adhesion Molecules: Druggable Targets for Modulating the Connectome and Brain Disorders?

The human brain develops and modulates more than a trillion connections in ways that depend fundamentally on ligand recognition mediated by cell adhesion molecules (CAMs). These cell surface proteins display single transmembrane, GPI-anchored and other configurations (Li *et al*, 2009). Products of at least 500 human CAM genes transduce information about ligands expressed by neighboring cells and extracellular matrix, altering cellular signaling and morphology. Understanding the CAM language for establishing and shaping brain connections is key to understanding the connectome.

Common variants in CAM genes have been associated with many human brain and neuropsychiatric disease phenotypes, largely based on modest contributions of multiple genomic variations within each of these genes. Such genetic architecture is unsatisfying for efforts to establish statistically ironclad associations, but is consistent with the likely importance of and selective pressure on the roles that CAMs play. Addiction, abilities to quit smoking, schizophrenia, autism, ADHD, RLS/Willis Ekbom syndrome, cerebral cortical volume and memory provide a sampling of phenotypes associated with variation in CAM genes (Schormair *et al*, 2008; Uhl *et al*, 2008). Decoding the language of CAMs is thus also essential to understanding many brain disorders and phenotypes.

Tests of a growing number of mouse models of altered CAM expression support many of their associations with human disorders and phenotypes. Altered expression of individual CAMs can provide relatively selective effects (Ishiguro *et al*, 2006). More devastating phenotypes can follow simultaneous deletion of several related CAMs (Uetani *et al*, 2006), supporting functional redundancies provided by multimember CAM families. The overall constellation of phenotypes from mice with altered expression of single CAM genes supports the idea that many CAM 'antagonists' (or 'agonists') might modulate brain connections and activities with modest overall toxicities/side effects and favorable therapeutic indices.

An example: CDH13 and PTPRD are CAMs that share human associations with addiction, haplotypes that influence levels of human brain expression and expression in addiction-related neuronal circuits (Uhl *et al*, 2008). Humans with selected CDH13 and PTPRD haplotypes and mice with reduced expression display altered dose–response relationships for psychostimulant reward (JD and GRU, submitted). Heterozygote knockouts that approximate the level-of-expression differences identified in humans display few systemic pathologies.

Should we thus think about CDH13, PTPRD, and other CAMs as potentially druggable targets for modulating brain phenotypes, establish robust screening assays, test libraries of small-molecule ligands for *in vitro* effects, and test for *in vivo* effects of lead and more optimized structures? Availability of good crystal structures for CDH13 (Ciatto *et al*, 2010) and a number of CAMs could aid this effort. Information about naturally occurring membrane bound, matrix, and soluble CAM ligands will help. Small molecules that recognize members of several of these CAM subfamilies, often identified based on their potential antitumor properties, can provide valuable starting points. Disease association and mouse model data can provide targets and estimates of potential toxicities. Data for the detailed pattern of CAM expression in brain, and in other organs, can also help us to estimate the specificity of possible CAM ligands. Studies in conditional knockout mice will help to define the contributions of developmental *vs* adult CAM expression to disease phenotypes. Improving currently spotty understanding of the intracellular signaling consequences of CAM–ligand interactions will aid CAM targeting.

Our answer is thus yes. CAMs may be among the most promising and understudied druggable targets for modulating the connectome and influencing brain disorders.

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Circuits in Sync: Decoding Theta Communication in Fear and Safety

Theta-frequency (4–12 Hz) oscillations were first isolated and came of age as an important concept in neurophysiology in the dorsal hippocampus