LRRs: A platform to build a Protein Recognition Motif

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The leucine-rich repeat domains (LRRs) of cell-surface receptors often constitute the binding regions for small protein ligands. Examples are found in many types of medically important receptors, e.g. Insulin and growth-factor receptors, G-coupled protein receptors and Toll-like receptors. Thus they are important therapeutic targets.

The architecture of LRRs generally consists of a β-helix or solenoid with a prominent β-sheet down one face forming the ligand-binding surface. Side chains on this face are tightly packed to form a sterically well-defined surface with the chemical composition dictated by sequence. The opposite face shows considerable structural variability and here, the space occupied by the main chain appears to dictate the curvature of the ligand-binding face. Thus LRRs have a simple but elegant design, where the main chain provides a regular framework of variable size and shape and chemical nature of the site is under genetic control.

Now that a considerable number of these structures have been determined, with or without their ligands, a detailed analysis has revealed the factors which control the overall architecture for *ab initio* design of a protein-binding surface. Naturally-occurring augmentations of this standard architecture provide additional ways of creating a protein-docking site.

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