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pharmacological perspectives from biology, chemistry and genomics

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DEPARTMENTS

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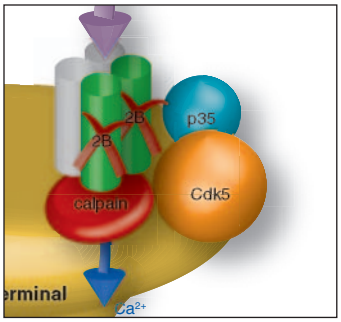
VIEWPOINTS

246 Cdk5 in Memory: The Good and Bad of It



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"Burnt-out Ends of Smokey Days"?

In the adult brain, cyclin-dependent kinase 5 (Cdk5) can be beneficial by contributing to memory formation or can be detrimental by causing neurodegeneration, and it is of great interest to understand this dichotomy. Currently, it remains largely unknown which mechanisms are regulated by Cdk5. Recent studies by Hawasli et al. and Qu et al., however, are significant advances towards mechanistic insights. Hawasli et al. demonstrate that Cdk5 regulates protease-directed degradation of an important synaptic receptor, which impacts memory formation. Qu et al. show that Cdk5 inhibits the activity of an enzyme that metabolizes reactive oxygen species, which then leads to neurodegeneration. These two studies hold promise for establishing treatments to prevent cognitive dysfunction and neurodegeneration.

Karl Peter Giese

249 Regeneration: Bringing Together Different Disciplines

Research into tissue repair and regeneration is fought on many fronts. This article emphasizes that research into therapeutic tissue regeneration depends on diverse concepts and approaches. The interface between classical animal models, such as invertebrates and newts, and new opportunities, such as those afforded by mammalian stem cells, is in many respects unexpected. But this interface may make a reality of medicine's long-held dreams for tissue regeneration and organ replacement.

Panagiotis A. Tsonis

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Of stem cells, scaffolding, and dedifferentiation

REVIEWS

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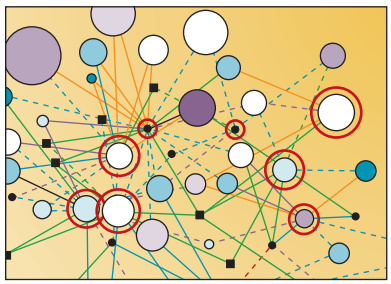
Reaping the rewards of natural products

Predatory cone snails (genus *Conus*) produce a rich array of venoms that collectively contain an estimated 100,000 small, disulfide-rich peptides (i.e., conotoxins, or conopeptides). Over the last few decades, the conopeptides have revealed a remarkable diversity of pharmacological function and utility. An evolutionary rationale for the existence of such a large and pharmacologically diverse set of gene products can be premised on the complexity of intra- and interspecies interactions that define the ecology of *Conus* snails. Insights into these evolutionary trends, moreover, have been exploited with great neuropharmacological success, so that research into the *Conus* snails effectively recapitulates a new concerted discovery approach, which we discuss here, for developing unique ligands for both laboratory and therapeutic applications. The *Conus* peptides thus serve as a model system for reaping the pharmacological potential of biodiverse animal lineages.

Baldomero M. Olivera and Russell W. Teichert



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More to Alzheimer disease than amyloid β

The precise pathological events that cause cognitive deficits in Alzheimer disease remain to be determined. The most widely held view is that accumulation of amyloid β peptide initiates the disease process; however, with more than eighteen amyloid-based therapeutic candidates currently in clinical trials, the targeting of amyloid alone may not be sufficient to improve functional deficits over the course of the disease. Alternative targets, such as the tau protein and apolipoprotein E, have thus been increasingly investigated, and in the future, therapeutic strategies will likely address events that are upstream of a more broadly construed pathological cascade that includes but is not limited to the generation and accumulation of amyloid β. Consideration of such events lays the basis for an "indirect amyloid hypothesis," for which data are beginning to emerge. Although it is clinically defined by simple post-mortem criteria, Alzheimer disease likely has a complex etiology, and effective treatments for this disease will become ever more urgent as the world's population ages.

Guy R. Seabrook, William J. Ray, Mark Shearman, and Michael Hutton