

Ingenuity[®] Science Spotlight:

Articles featured in the Ingenuity Science Spotlight represent some of the best and most diverse examples of how IPA[®] has contributed to research across multiple platforms, research areas, and research goals.



"IPA is a fast and powerful tool in the analysis of results of functional screens. It has been a great help to us in building networks of the hits that were identified in our siRNA screen. Based on these analyses, we were able to direct our follow-up experiments leading to meaningful results and valuable insights."

Roderick Beijersbergen, Ph.D
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Intracellular bacterial growth is controlled by a kinase network around PKB/AKT1.

Kuijl C, Savage ND, Marsman M, Tuin AW, Janssen L, Egan DA, Ketema M, van den Nieuwendijk R, van den Eeden SJ, Geluk A, Poot A, van der Marel G, Beijersbergen RL, Overkleeft H, Ottenhoff TH, Neeffjes J. *Nature*, 2007 Nov 29;450(7170):725-30.

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=18046412&ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

In the November 29th issue of *Nature*, a team of scientists from The Netherlands Cancer Institute described their novel approach for identifying compounds for controlling host-specific biochemical pathways that are essential for bacterial growth. By utilizing an RNAi screen of the human kinome, the team identified host kinases that affect intracellular growth of *Salmonella typhimurium*. Analysis of positive hits from the kinase screen in the context of IPA's extensive network of molecular interactions, regulatory events, and post-translational modifications revealed a single network clustered around AKT1, suggesting a critical role for this molecular module in intracellular *S. typhimurium* growth. In follow up studies, AKT1 inhibitors prevented intracellular bacterial growth in *S. typhimurium*-infected cell lines and prolonged survival of infected mice. Interpretation of RNAi screen results in IPA is an integral part of their overall strategy for developing new antibiotics that target host signaling networks necessary for pathogen survival.

Initial studies in which kinase inhibitors were shown to affect intracellular salmonella growth in MCF7 cells led the team expand their search and design an siRNA screen to identify additional host kinases that were responsible for controlling intracellular growth of various pathogens. RNAi effects on *S. typhimurium* growth were monitored with automated microscopy. Positive hits from the screen (host kinases) were then analyzed in IPA. Because IPA incorporates biological interactions and context beyond the scope of the initial assay hits, researchers are able to generate testable hypotheses and design follow up experiments to determine which additional kinases may affect intracellular growth of bacteria. IPA also identifies chemicals that are known to inhibit those targets, providing quick links to tools that can chemically perturb that network. In this way IPA provides a means for identifying a target network (or

pathway) that can serve as a model to test the feasibility of using specific kinase inhibitors as antibiotics, as well as understand the potential mechanism of action of novel antibiotics.