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An accelerated translational research: From a phenotype to a drug candidate

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Over the past few decades, necrosis has gradually been verified as an important pathway of programmed cell death, playing essential roles in ovulation innate immunity, and inflammation in metazoan animals. Programmed cell necrosis is associated with lethal diseases such as ischemia brain/kidney damage, atherosclerosis, myocardial infarction, pancreatitis, and systemic inflammatory response syndrome (SIRS). Thus, targeting necrosis pathway can offer a new opportunity for treating these diseases. So far, three important signaling proteins, receptor-interacting protein 1 (RIP1), receptor-interacting protein 3 (RIP3), and mixed lineage kinase domain-like protein (MLKL), have been recognized as critical components in the regulated necrotic cell death pathway. With purposes of finding new targets involved in this pathway and developing new reagents for related diseases treatment, we carried out Phenotypic screening to a library of 300 thousand compounds, discovered a few screening hits. We have improved their bioactivity to subnanomolar necrosis inhibitors through medicinal chemistry effort, identified their biological interacting targets by applying chemical genetic methods and chemical biology. By far, we have developed different series of selective inhibitors against human RIP1, RIP3 and MLKL respectively, we have successfully advanced our RIP1 inhibitors into several animal disease models, achieved 100% protection on mouse shock model induced by TNF-α comparing to 50% survival rate in untreated group, remarkable protecting effect on Ulcerative Colitis, and profound result on preserving the fertility of mice at an Advanced Age.

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