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Reverse translation in cardiovascular drug discovery

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Abstract

During the last decade, approval of new drugs decreased in spite of significant increase in R&D spending. The reasons for compound attrition will be discussed. A part of potential solution is the focus on “reverse translation” when clinical data are translated back to the pre-clinical drug discovery space. I will provide specific examples of learning from failed clinical trials (CETP inhibitor), from human genetics (PCSK9) and from human pathophysiology. The latter is exemplified by the importance of local blood flow patterns making certain areas of human arterial tree prone to development of atherosclerosis. In collaboration with a biotech company HemoShear, we have applied these fluid dynamics patterns in a co-culture of primary human endothelial and smooth muscle cells to test vascular effects of GLP-1 (7-36) and its degradation products. Local hydrodynamics combined with high glucose and inflammatory stimuli affected expression of GLP-1 receptor in vitro. DPP4-induced degradation product GLP-1(9-36) prevented smooth muscle cell apoptosis in the pro-atherogenic environment. These effects were missed in the static cell culture conditions. Thus, learning from the clinical studies (“reverse translation”) provides value for drug discovery and improves potential for the “forward translation” from bench to the bedside.

Biography

Mark D. Rekhter received his Ph.D. in 1987 at the 2nd Moscow Medical Institute (Russia) and followed up with a postdoctoral training at the University of Washington and University of Michigan (USA). Currently, he is a Senior Research Advisor at the Lilly Research Laboratories, Eli Lilly and Co. Dr. Rekhter leads pre-clinical drug discovery teams in the area of cardiorenal complications of diabetes. Recently, he received Lilly Research Laboratories President’s Scientific Award (the highest recognition given at Eli Lilly and Co for scientific achievements).