Translational Neurogastroenterology: from Basics to Clinical Applications

Emeran A. Mayer, M.D., Ph.D.

UCLA Center for Neurobiology of Stress, Division of Digestive Diseases, David Geffen School of Medicine at UCLA, Los Angeles, USA

Background: During the past decade, there has been a dramatic increase in the number of publications in the area of Neurogastroenterology, ranging from basic studies on molecular mechanisms preclinical in vivo studies, and to studies in humans.

Results: In the case of functional GI disorders, several preclinical animal models have been reported, which show alterations in visceral sensitivity and intestinal motility. Despite face and construct validity of several of these models, their ability to predict effectiveness of candidate drugs for irritable bowel syndrome has been disappointing. Similarly, several experimental medicine models have been reported with good validity for IBS, but the predictive validity for effectiveness of new compounds to effectively treat IBS symptoms has been disappointing. In order to improve the translational effectiveness of drug development, novel approaches are being developed to 1) identify and characterize the neurobiological mechanisms (endophenotypes) underlying functional GI disorders, and find associations of these endophenotypes with genetic and environmental vulnerability factors; 2) Model these endophenotypes in rodent models, and verify the effect of candidate genes on these endophenotypes; 3) Use the most robust endophenotypes with the greatest effect size on the human syndrome for drug development.

Conclusions: Despite the scientific breakthroughs of Neurogastroenterology, translational success for human disorders has been very modest. Novel strategies are required to overcome this limitation.

Key words: Functional GI disorders, Disease models, Endophenotypes