

CHAPTER 1

Discovery and Clinical Validation of HCV Inhibitors Targeting the NS5A Protein

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1.1 Introduction

Significant effort has been invested in elucidating the exact role and function of the NS5A protein in the hepatitis C virus (HCV) replication cycle. Although, unlike the NS3 and NS5B proteins, no enzymatic function has been identified thus far for NS5A, it has become apparent that this protein plays a diverse and critical set of roles both in the replication of the virus and in the mediation of host–virus interactions. Despite its multifunctional role, the lack of a well-characterized function coupled with the limited availability of structural information, compared with the NS3 protease and NS5B polymerase, initially made the NS5A protein a less compelling target for therapeutic intervention. That changed, however, with the validation of NS5A as a clinically relevant target by daclatasvir (**1**), where single doses effected pronounced and rapid declines in viral RNA in HCV-infected subjects (Figure 1.1).¹ Highlights of the