「第 36 回メディシナルケミストリーシンポジウム」講演要旨集

＜正誤表＞

・12 ページ　全体プグラム（第３日目）招待講演７…演題変更

（誤）

10：30 ～ 11：10　座長：田中　大輔（Exscientia）
招待講演 7　**The Discovery of Niraparib, a Novel Oral PARP inhibitor for the Treatment of Tumours with Defects in Homologous Recombination.**
Michael Rowley（IRBM，Pharmaron Drug Discovery Services Europe）

・12 ページ　全体プグラム（第３日目）招待講演７…演題変更

（正）

10：30 ～ 11：10　座長：田中　大輔（Exscientia）
招待講演 7　**The Discovery of the Macrocyclic HCV NS3/4A Protease Inhibitor Grazoprevir (MK-5172).**
Michael Rowley（IRBM，Pharmaron Drug Discovery Services Europe）

・38 ページ　招待講演要旨　招待講演７…講演要旨差替

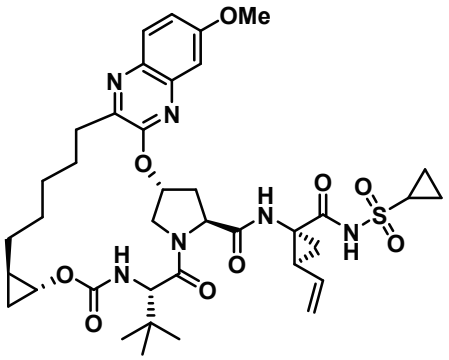
次ページ参照

第 36 回メディシナルケミストリーシンポジウム 実行委員会

The Discovery of the Macrocyclic HCV NS3/4A Protease Inhibitor Grazoprevir (MK-5172).

Michael Rowley[1, 2]

1. *IRBM, Via Pontina Km 30,600, 00040 Pomezia, Rome, Italy*
2. *Current address: Pharmaron Drug Discovery Services Europe, Hertford Road, Hoddesdon, EN11 9BU, United Kingdom*



Grazoprevir

Hepatitis C Virus (HCV) is a world health problem with approximately 2% of the population affected. Viral infection is chronic and can cause severe health issues including chronic liver disease, cirrhosis, need for liver transplant and, ultimately, death.

HCV has significant genetic heterogeneity with six major genotypes, multiple subtypes and a high propensity for mutations leading to drug resistance. Given this, targeting the virus with combination treatment using different viral targets is the approach most likely to lead to viral suppression and cure.

HCV NS3/4A protease is a target of long standing interest. It has proved to be a very challenging target, with a large shallow binding site meaning that compounds with high affinity have needed to be large. Alternatively affinity can be gained by covalent inhibition, and the first marketed protease inhibitors used this covalent mechanism.

In our project we searched for a non-covalent inhibitor, using structure based design and innovative chemistry to discover compounds with novel structures that potently inhibited the protease. After early success with this approach we set ourselves the challenging target of obtaining the broadest possible genotype and mutant coverage possible, in order to be able to treat a wide variety of patients.

The talk covers the strategy we adopted, key findings in terms of genotype and resistance coverage, medicinal and synthetic chemistry approaches, and challenges associated with the project. This led to the discovery of grazoprevir which, as a fix dosed combination with elbasvir was approved by the FDA in 2016.