疾患プロテオゲノム研究センター
ゲノム制御学セミナー　**NO. 9**

日時：**2015** 年 **4** 月 **13** 日（月）**17:00~18:30**
場所：疾患プロテオゲノム研究センター1F　交流ホール

# Dr. Laurent Désaubry

CNRS Research Director,
CNRS-Strasbourg University, France

## Development of novel anticancer agents that target prohibitins and the translation initiation factor eIF4a

Laurent Désaubry 博士はフランスのストラスブール大学にて創薬化学(medicinal chemistry)を専門とし、これまでに細胞の生存・代謝・炎症に関連する様々なシグナルを制御するシャペロンタンパク質である prohibitins(プロヒビチン)や翻訳開始因子 eIF4a を標的とした化合物による創薬を目指し、特に抗がん剤の開発を精力的に進めています。本セミナーでは、prohibitins および eIF4a を標的とした新しい抗がん剤開発について講演して頂きます。多数のご参加をお待ちしております。

Future Med. Chem. 5, 2185-97 (2013)
J. Med. Chem. 54, 411–415 (2011)
PLos One 6, e25302, (2011)
Chem. Biol. 20, 316–331 (2013)
J. Med. Chem. 52, 5176–5187 (2009).
J. Med. Chem. 55, 10064–10073 (2012).
Chem. Biol. 19, 1093-104 (2012).
Nature 513, 105–109 (2014).

■ 講演要旨につきましては裏面をご参照下さい。

**なお、本セミナーは大学院医科学教育部特別講義を兼ねています。**
**大学院生、教員、学部学生等、興味を持つ全ての方のご来聴を歓迎致します。**

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**17:00-18:30 Monday 13th April, 2015**

**1F Seminar Hall Institute for Genome Research, Kuramoto Campus**

# Development of novel anticancer agents that target prohibitins and the translation initiation factor eIF4a


## Dr. Laurent Désaubry, CNRS Research Director

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***Abstract***

Flavaglines are a family of anticancer natural products that relieve the resistance to cancer chemotherapies and display a strong cytotoxicity that is specific to cancer cells in a low nanomolar range.[1-4] Not only flavaglines are not toxic to non-cancer cells, but they protect normal cells from various stresses. Thus, we demonstrated for the first time that these compounds protect the heart and neurons from the adverse effects of cancer chemotherapies involving anthracyclines and cisplatin.[4,5]

We also identified the scaffold proteins prohibitins-1 and -2 (PHB1/2)[6] as the molecular targets of flavaglines.[7] We demonstrated that the binding of flavaglines to PHBs prevents interaction between PHBs and CRaf and, thereby, inhibits CRaf activation and subsequently CRaf-MEK-ERK signaling, which is critical to survival and proliferation of cancer cells.[6]

Flavaglines also directly inhibit another emerging target in oncology, the translation initiation factor eIF4a. *In vivo* data indicate that flavaglines could greatly improve the treatment of chemoresistant metastatic melanoma.[8]


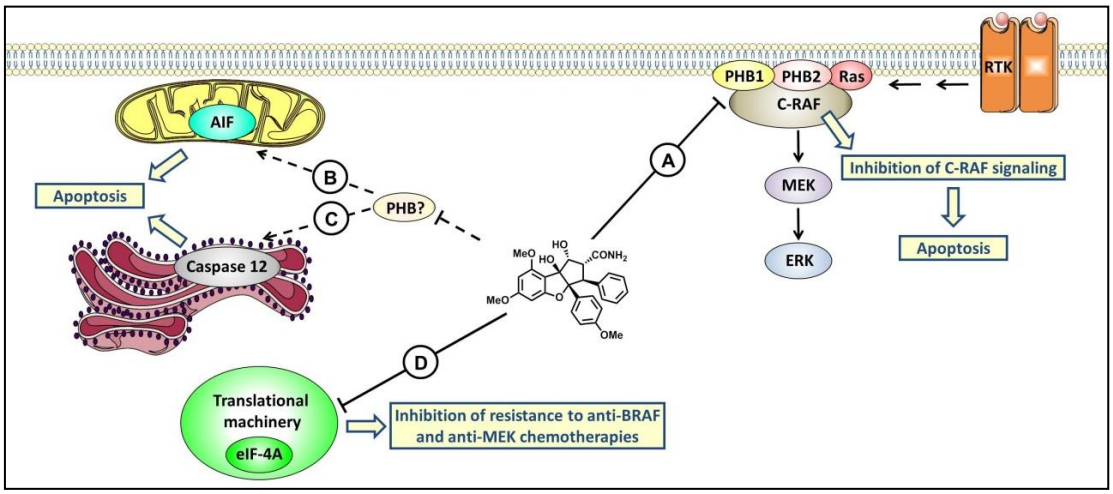


**Figure.** Anticancer mechanisms of flavaglines. (**A**) Inhibition of the activation of CRAF by Ras. (**B**,**C**) Translocation of AIF and caspase-12 to induce apoptosis. (**D**) Inhibition of eIF4A overcoming resistance to therapies targeting BRAF or MEK.

**References:**


**1.** *Future Med. Chem*. 5, 2185-97 (2013).
**2.** *J. Med. Chem.* 52, 5176–5187 (2009).
**3.** *J. Med. Chem.* 54, 411–415 (2011).
**4.** *J Med Chem* 55, 10064–10073 (2012).
**5.** *PLos One* 6, e25302, (2011).
**6.** *Chem. Biol*. 19, 1093-104 (2012).
**7.** *Chem. Biol*. 20, 316–331 (2013).
**8.** *Nature* 513, 105–109 (2014).