# Allosteric inhibitors of the NS3 protease from the hepatitis C virus with a new action mechanism

Instituto Aragonés de Ciencias de la Salud

Instituto Universitario de Investigación Biocomputación y Física de Sistemas Complejos
Universidad Zaragoza

araid
FUNDACIÓN AGENCIA ARAGONESA PARA LA INVESTIGACIÓN Y EL DESARROLLO

Zaragoza, 6 de junio de 2012

# Content

1. **The Research Group**
2. **The Product**
   a) Target indications
   b) Innovative mechanisms of action
   c) Differential features facing the market
   d) Current status of development
   e) IPR protection
   f) Pitfalls & Risks to be considered
3. **Partnering Opportunities**

# Content

# The Research Group

**Origin:** 2004

Institute of Biocomputation and Physics of Complex Systems (BIFI), Universidad de Zaragoza

Protein Biophysics & Biochemistry Laboratory

Pharmacological and Biotechnological Targets

**Resources:** Infrastructures at BIFI: Molecular Biology Techniques

Spectroscopy (CD, Abs, Fluo,...)

Calorimetry

X-Ray Diffraction

High-Throughput Screening

Computation

# The Research Group

## Technological Skills:

- Target Cloning and Expression
- Target (Structural and Functional) Characterization
- Bioactive Compounds Identification
- Efficacy and Toxicity Cell Assays
- Ligand Optimization

# The Research Group

**Projects:**

NS3 Protease from HCV:

- MICINN: 2004-2007; **BFU2010-19451 2010-2013**
- DGA: 2009-2011
- FIS: **PI10/0186 2011-2013**
- Unizar: 2010

**Institutions:**

- Universidad de Zaragoza
- Instituto Aragonés de Ciencias de la Salud (I+CS)
- Fundación ARAID

# Content

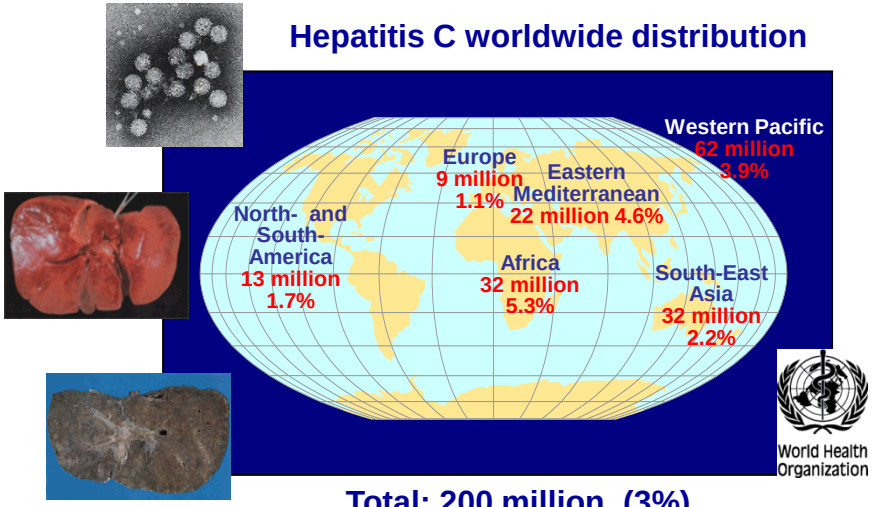
# The Product

## *a) Target indications*

**Hepatitis C Treatment**

# The Product

## a) *Target indications*




**Total: 200 million (3%)**

**3 a 4 million of new infected each year**

**Hepatitis C Worldwide Relevance**

# The Product

## *a) Target indications*

**Difficulties in Hepatitis C Management**

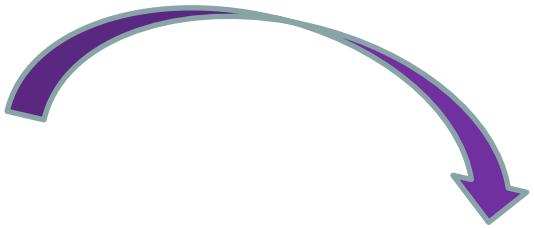
1. **High incidence (3%)**
2. **Difficult diagnosis**
3. **No vaccines**
4. **Drug resistance mutations**
5. **Severe side-effects and low adherence in current treatment**

# The Product

## *a) Target indications*

**The final goal is to develop HAAT (Highly Active Antiviral Therapy)**

**Difficulties in Hepatitis C Management**



**New potent, selective, specific antiviral drugs with low resistance susceptibility to mutations are urgently needed for combination therapy**

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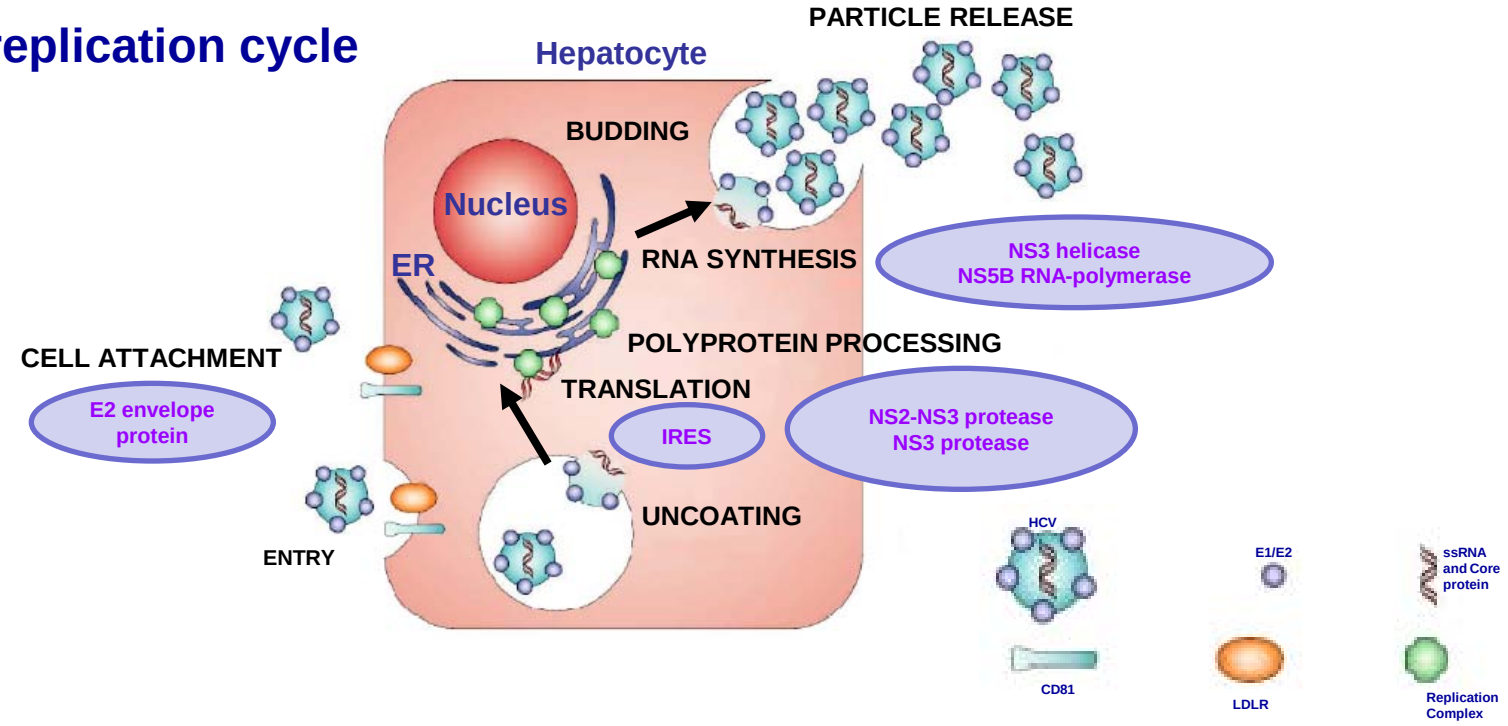
# The Product

## b) *Innovative mechanisms of action*

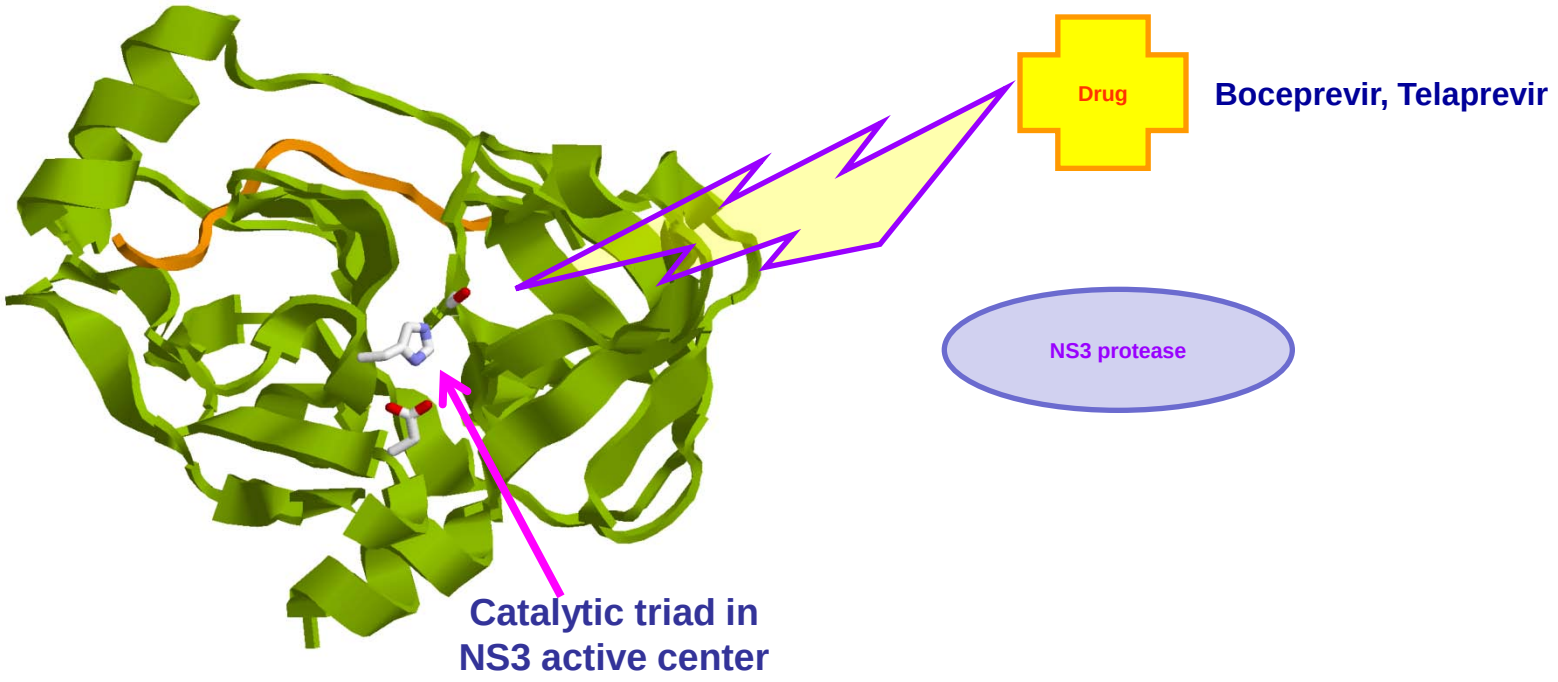
### VHC replication cycle



# The Product

## *b) Innovative mechanisms of action*

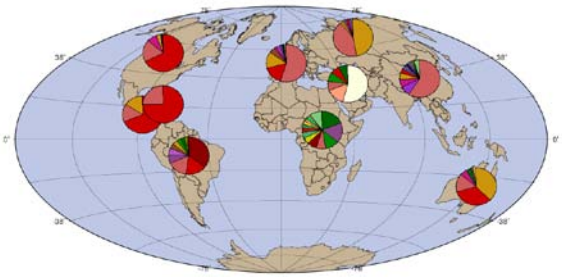
### Traditional Action Mechanism: Competitive Inhibitors of NS3 Protease

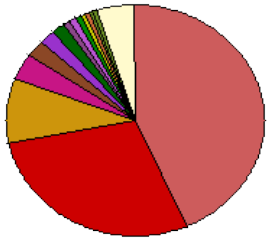


# The Product

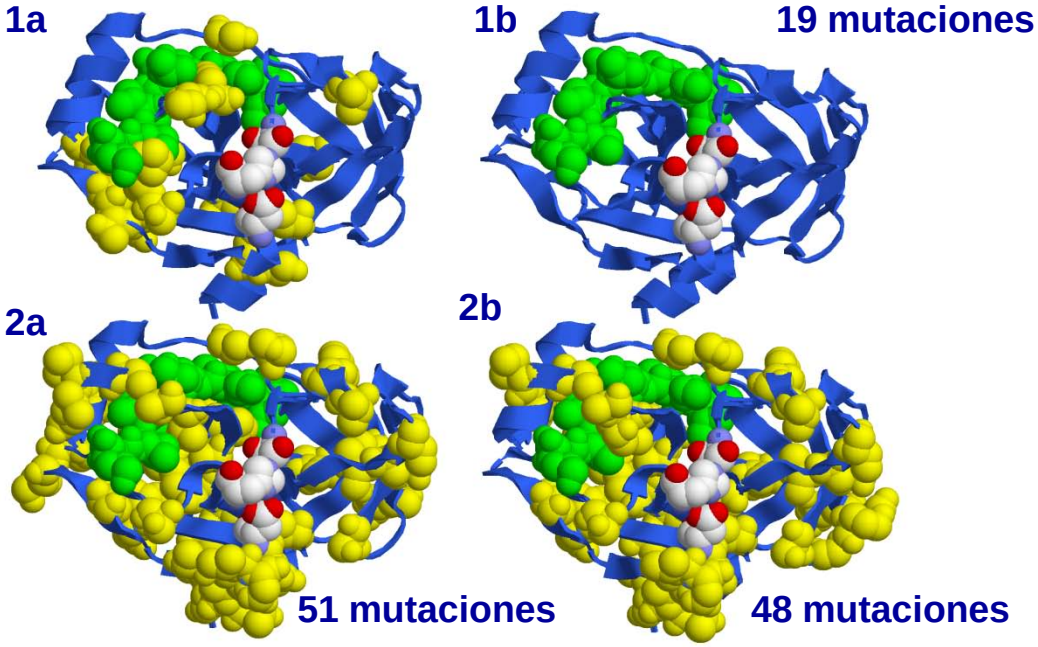
## *b) Innovative mechanisms of action*

**Problem with Traditional Mechanism: High Variability in HCV**






| | | |
|---|---|---|
| 1b | 7567 | 43.4 % |
| 1a | 4951 | 28.4 % |
| 3a | 1576 | 9.0 % |
| 2b | 651 | 3.7 % |
| 3 | 403 | 2.3 % |
| 2a | 345 | 2.0 % |
| 4a | 311 | 1.8 % |
| 2 | 154 | 0.9 % |
| 2c | 151 | 0.9 % |
| 4 | 123 | 0.7 % |
| 5a | 120 | 0.7 % |
| 3b | 88 | 0.5 % |
| 4d | 76 | 0.4 % |
| 6 | 70 | 0.4 % |
| other | 844 | 4.8 % |
| total | 17430 | 100.0 % |



# The Product

## *b) Innovative mechanisms of action*

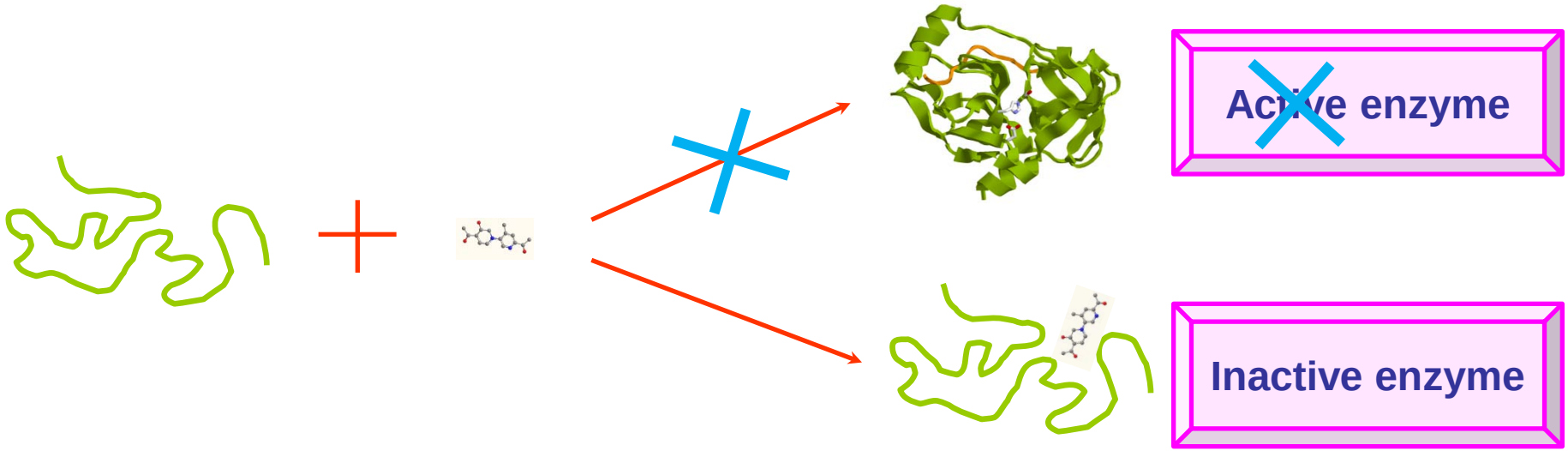
**Our Strategy: Allosteric Non-Competitive Inhibitors of NS3 Protease**

- **NS3 protease must adopt folded active conformation inside infected cells for successful viral life cycle**
- **NS3 protease exhibits a complex conformational landscape modulated by its interaction with two cofactors: viral accessory protein NS4A and $Zn^{+2}$**
- **Absence of $Zn^{+2}$ leads to global partial unfolding and inactivation**
- **Small molecules interacting with and stabilizing the $Zn^{+2}$-free conformation will trap the enzyme in an inactive state, blocking the viral life cycle**

# The Product

## *b) Innovative mechanisms of action*

**Our Strategy: Allosteric Non-Competitive Inhibitors of NS3 Protease**



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# The Product

## *c) Differential features facing the market*

**The identified compounds exerting this NEW ACTION MECHANISM present the following advantages:**

- **Low susceptibility to reported resistance mutations (different "target")**
- **Suitable candidates for combination therapy:**

  **interferon + ribavirin + current drugs + new antiviral compounds**

- **Re-profiling: ADMET information available**

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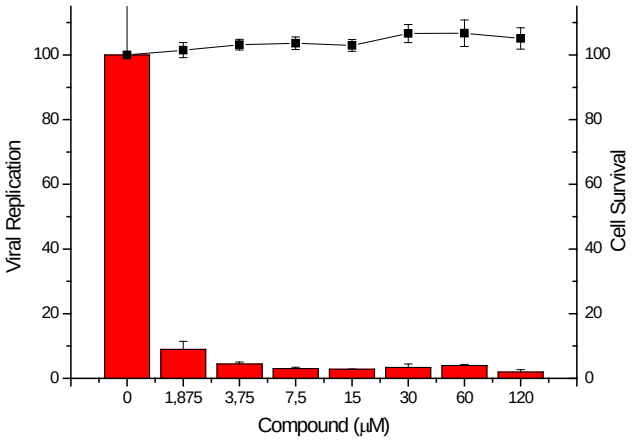
# The Product

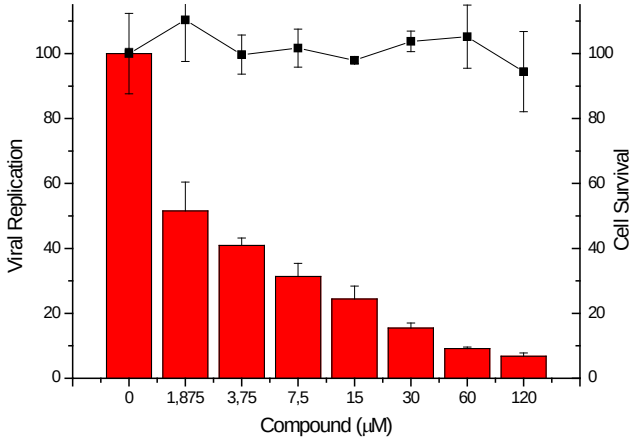
## *d) Current status of development*

- **Efficacy Cell Assays (using replicon system) mimicking the viral replication cycle in hepatic Huh 5-2 cell line)**
- **Toxicity Assays in hepatic Huh 5-2 and HeLa cell lines**
- **Biophysical studies on interaction with resistance-associated mutant NS3 proteases**

# The Product

## *d) Current status of development*



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# The Product

## *e) IPR protection*

**Patent Application Submission: 30 May 2012**

**Compounds + derivatives**

**Procedure for compound identification**

**Application number: EP12382218**

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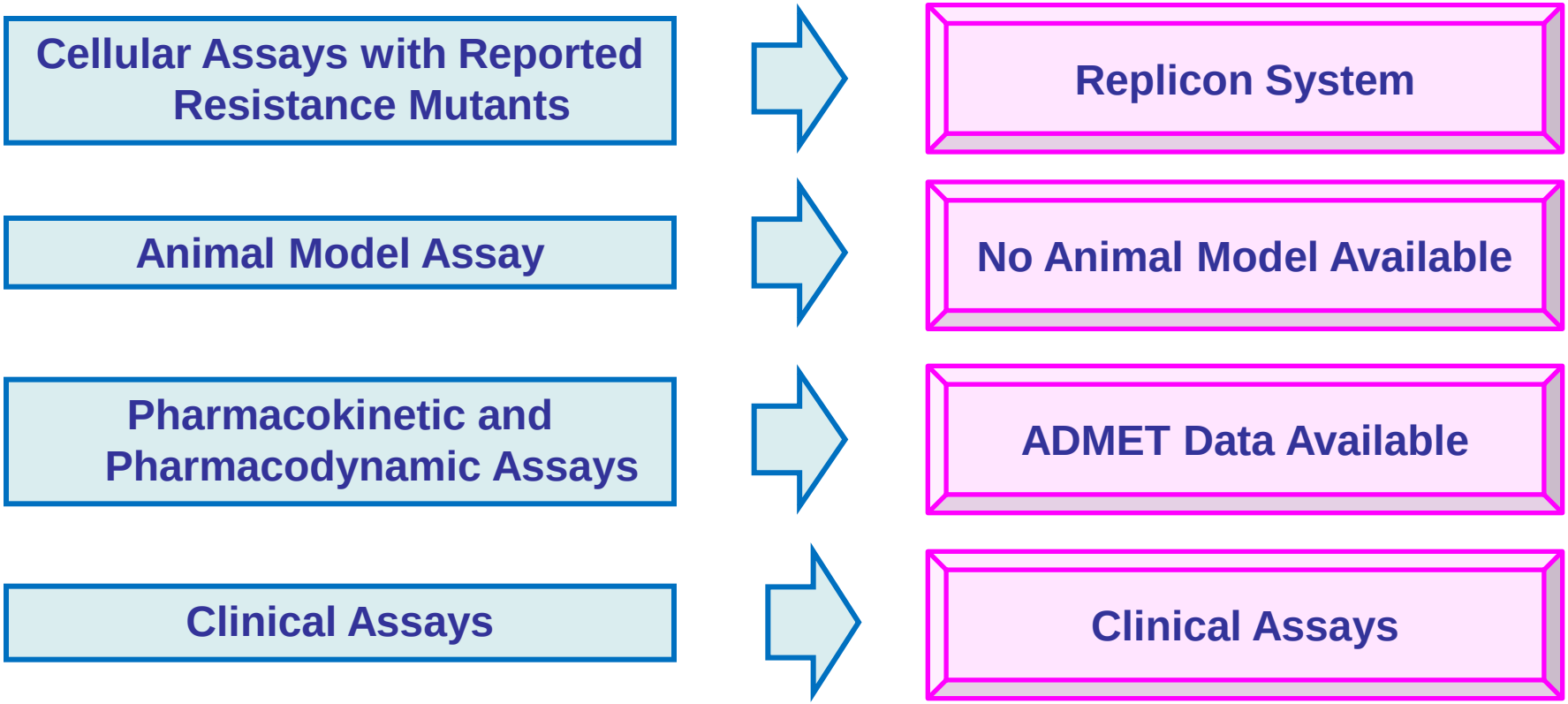
# The Product

## *f) Pitfalls & Risks to be considered*

**What follows?**



# Content

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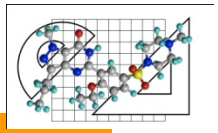
# Drug Discovery and Development

**Disease**

**Target Molecule**

***in vitro* Assays**

**Experimental and Computational Screening**



**Optimization**

**Preclinical Assays**

**Clinical Trials**

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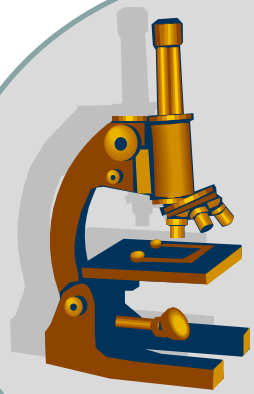
# Partnering Opportunities



Academia
Lab

Biotech and
Pharma

New approaches in

Drug Discovery

Identification of lead
compounds

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# THANK YOU FOR YOUR ATTENTION

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