HCV inhibitors
from bench to bedside

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This Talk will cover...

- **HCV** (epidemiology, genome, pathogenesis, treatment)
- **Drug Screening** (in vitro, bioinformatics)
- **Clinical trial**
HCV Prevalence

HCV in Kazakhstan (EHRN)
20-50% in high risk groups

Source: Center for Disease Analysis
HCV Pathogenesis

- **Acute HCV Infection**
  - Recovery: 15%-30%
  - Chronic HCV Infection: 70%-85%
    - Mild
    - Moderate
    - Severe
    - Cirrhosis: 15%-20%
      - End-Stage Liver Disease
      - Hepatocellular Carcinoma: 4%
      - Death: 4%
Treatment for HCV

PEGylated Interferon Ribavirin

Protease inhibitors

Boceprevir Telaprevir
2011

Simeprevir Sofosbuvir
2013

Ledipasvir Sofosbuvir Ombitasvir Paritaprevir Ritonavir Dasabuvir
2014

Polymerase inhibitors
Limitations of treatment

- PEGylated Interferon
- Ribavirin
- Long duration
- Adverse effects
- Affordability
- Resistance to treatment
- Subtype variation
HCV Genome

+ve ssRNA (9.6 kb)

Drug Targets
Helicase Action

Helicase

DNA

Trimeric complex

Inhibitor

UNWINDING
Drug Screening for HCV

- Cell Culture models
- Enzyme assays
- Bioinformatics
- Clinical trial
Drug Screening for HCV

- Huh8 cells
  - HCV Replicon

- Huh7 cells
  - HCV virion

- HCV NS3
  - Helicase
Drug Screening for HCV

1. Huh8 cells
   - HCV Replicon

2. Incubate cells with drug

3. Quantify HCV RNA

Graphs showing the effect of different drugs on HCV replication over time.
Drug Screening for HCV

Huh8 cells
HCV Replicon

Huh7 cells
HCV Virion

HCV NS3
Helicase
Drug Screening for HCV

Huh7 cells
HCV virion

Infect cells with HCV

Incubate cells with drug

Quantify HCV RNA
Drug Screening for HCV

Huh8 cells
HCV Replicon

Huh7 cells
HCV virion

HCV NS3
Helicase
Drug Screening for HCV

HCV NS3 Helicase

Purify viral helicase

Measure activity With and without drug
Docking Analysis

Bioinformatics
## Drug-Target Interactions

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Docking Energy (KJ/mol)</th>
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<tbody>
<tr>
<td></td>
<td>FlexX</td>
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<tr>
<td>Sparfloxacin</td>
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<td>Enrofloxacin</td>
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Summary

HCV NS3 helicase inhibitors:

- HCV replicon
- HCV virion synthesis
- HCV helicase
- Computer modeling
- Screening for novel inhibitors
IRFAN    SAEED
LAILA      HANI
SAMMER    ADIL
AFSHAN    SADIQ

CANCER & VIRUS LAB