Objectives

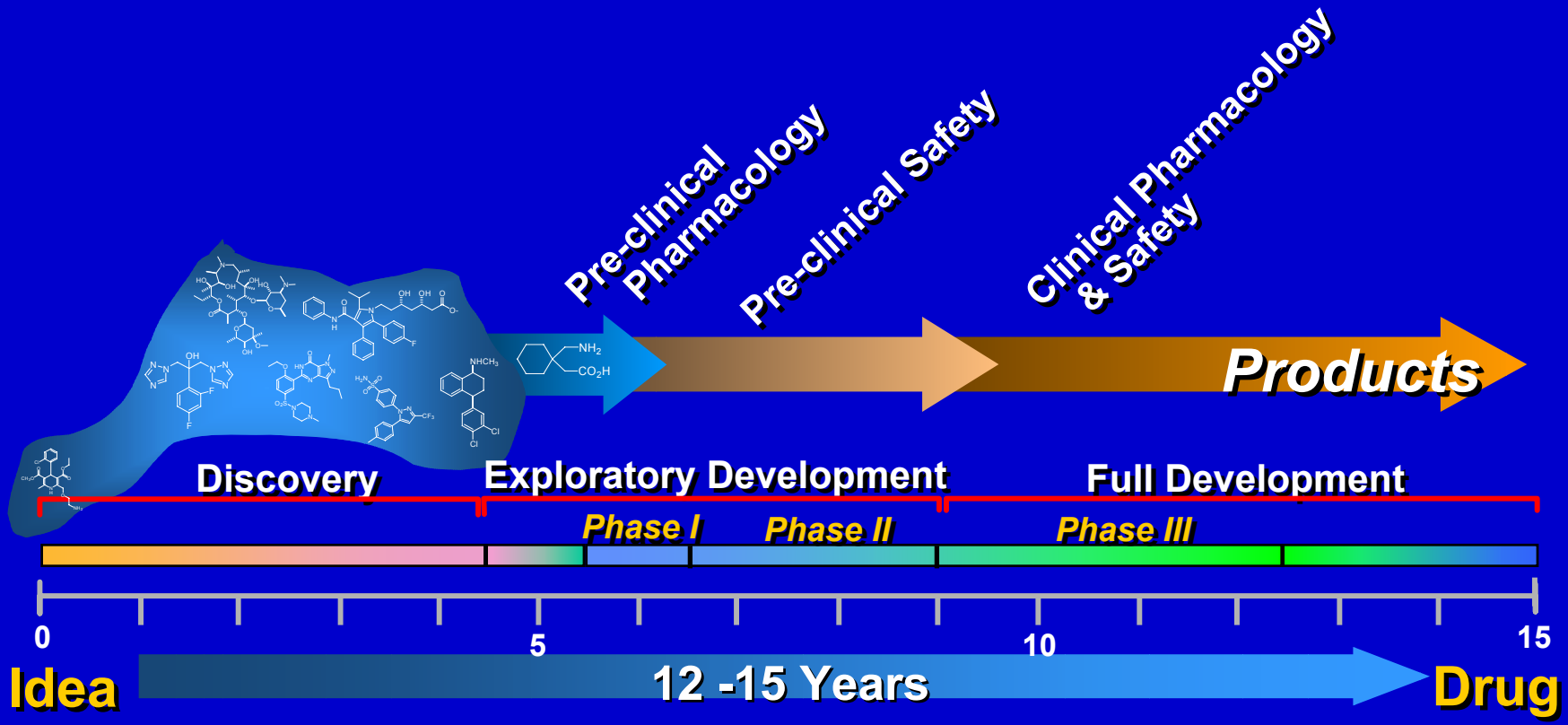
- Present scientific challenges of drug discovery
  - In general
  - In the HIV – MDR setting
- Case Studies – Capravirine and UK, 427-857

Not the Objective

- To review data on new drugs in development from Pfizer or anyone else

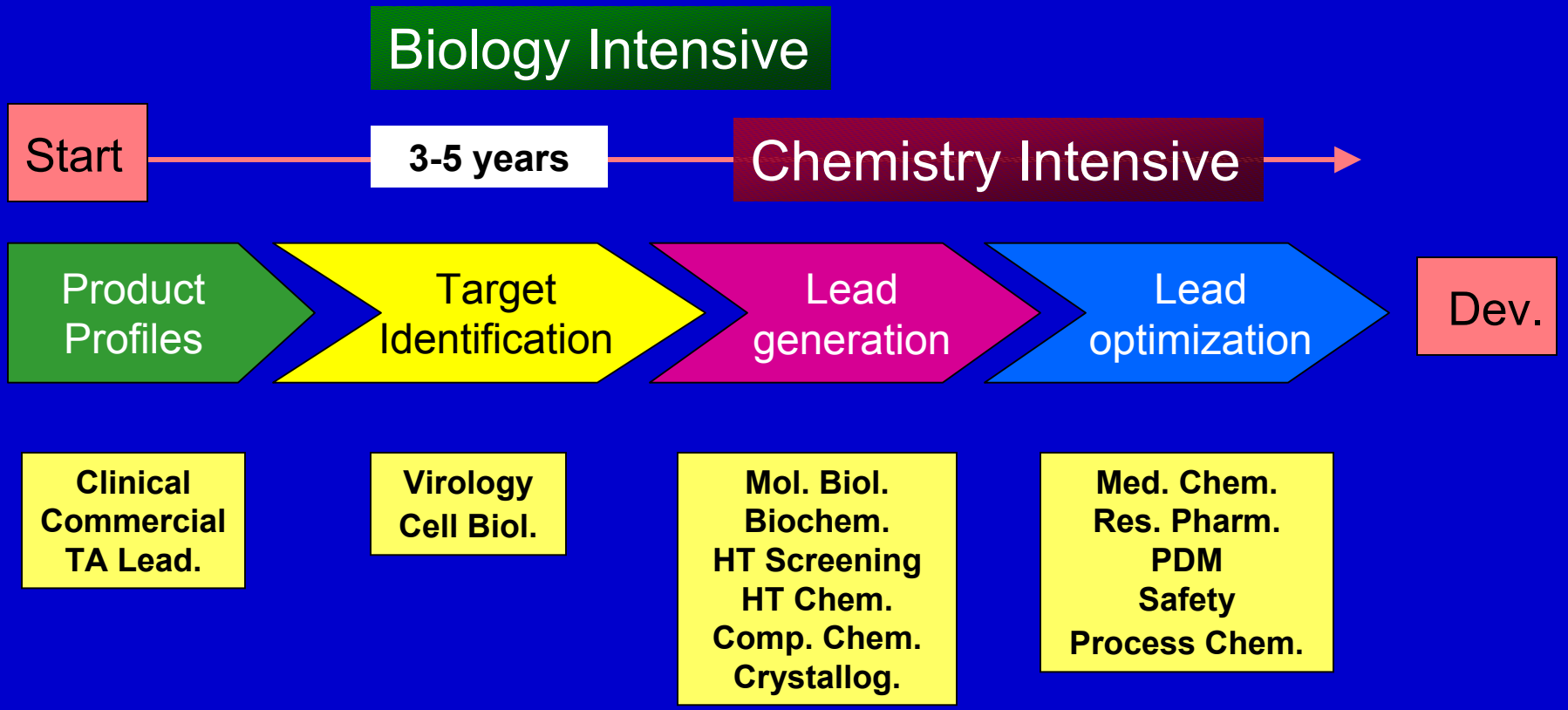
Drug Discovery/Development Pipeline

- Multifaceted, complicated, lengthy process



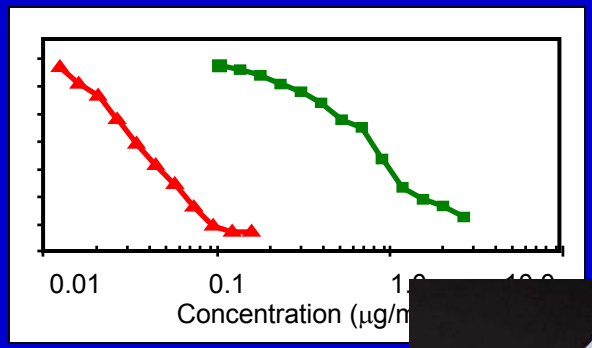
Drug Discovery Pipeline

- Multifaceted, complicated, lengthy process
- Up to 5 years to complete development transition



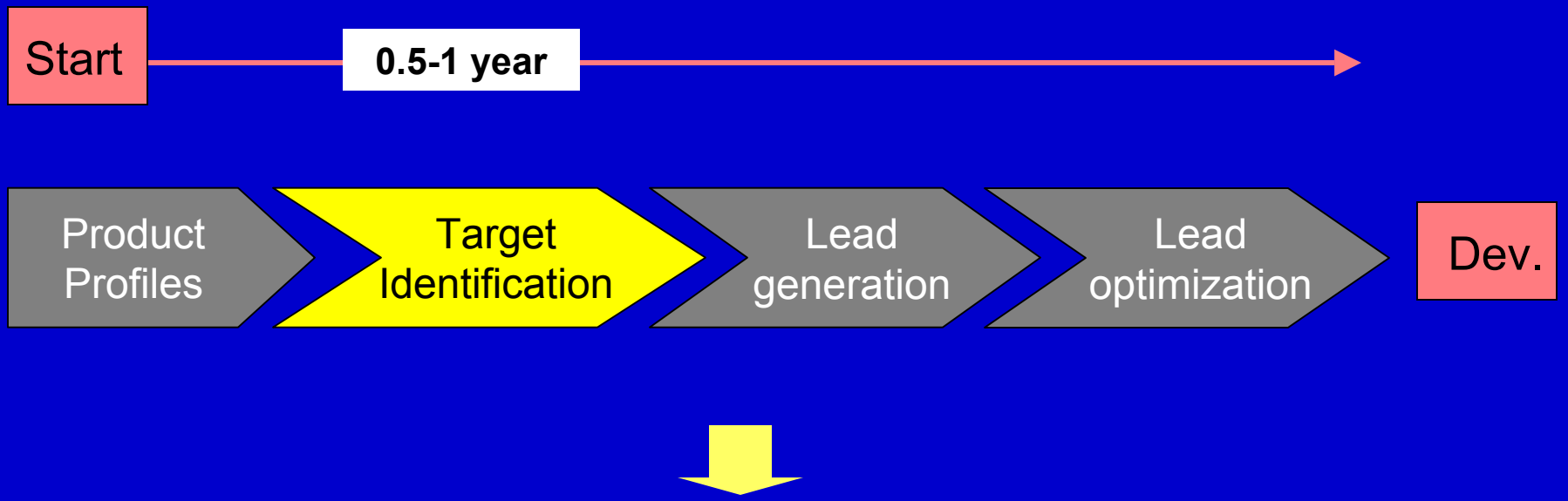
Patient/Product Profiles

- Identify areas of high unmet medical need
  - Sub-optimal or no existing therapies
- Identify differentiation basis for new therapy
  - potency/efficacy
  - resistance profile
  - dose size/frequency
  - safety/tolerability



Lab objectives which address desired profiles

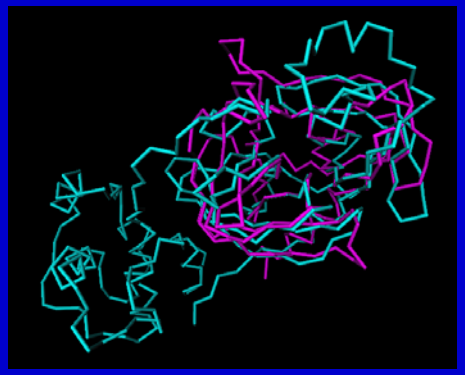
Drug Discovery Pipeline



- Biological entity associated with disease of interest (host or virus origin)
- Appropriate modulation of target anticipated to impact disease in manner consistent with product profile

Target Identification Criteria

- Activity/function essential for viral replication
  - Proven or inferred through biological experimentation
- Drugable target (subjective!)
  - Known small molecule inhibitors
  - Well defined active (binding) site
  - Historical success against related targets

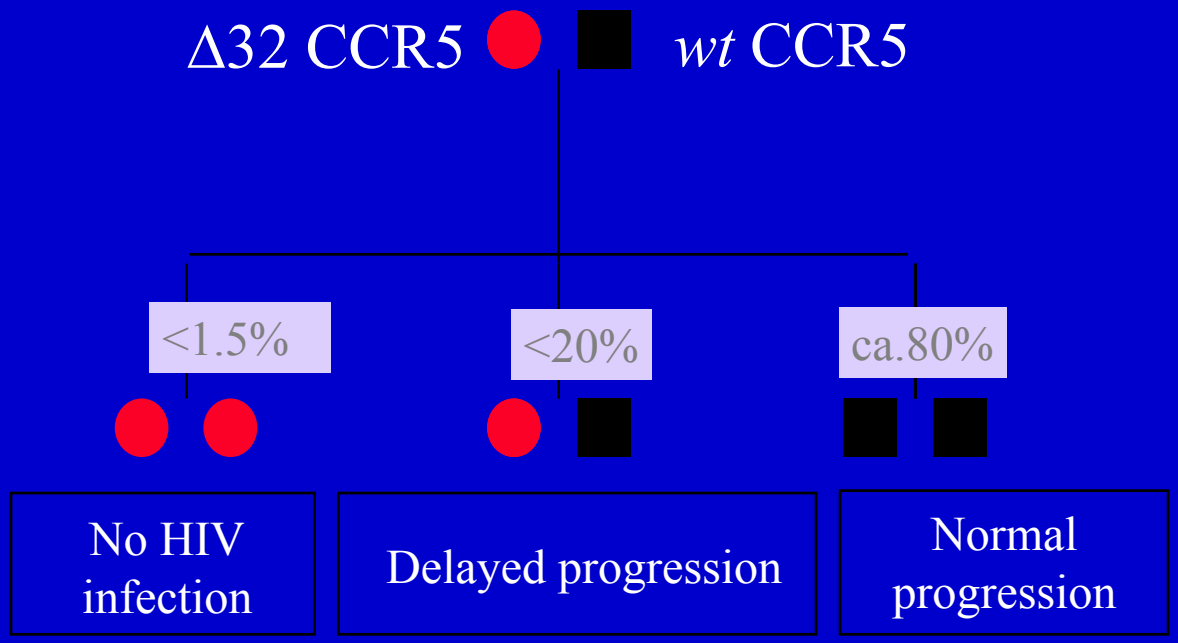


- Conservation across virus variants (where applicable)
- Selectivity vs human proteins

Difficult to incorporate all criteria in single target

CCR5 Validated in Humans ?

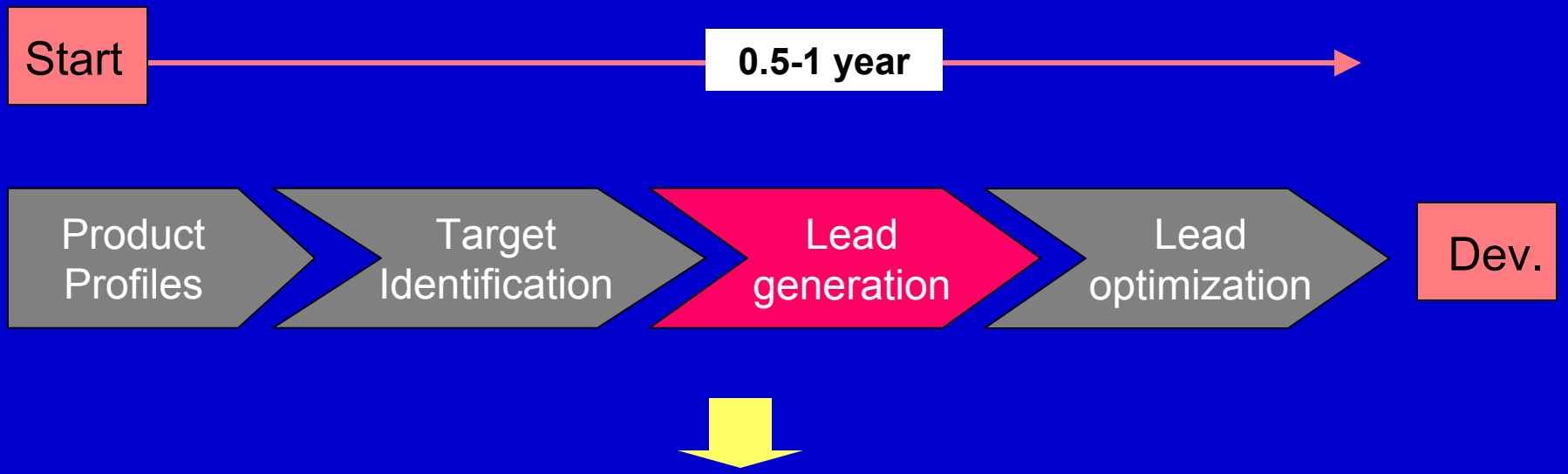
- Key co-receptor for HIV



- Validated for safety and efficacy

Liu *et al.*, 1996; Samson *et al.*, 1996; Dean *et al.*, 1996; Huang *et al.*, 1996; Michael *et al.*, 1997; Eugen-Olsen *et al.*, 1997

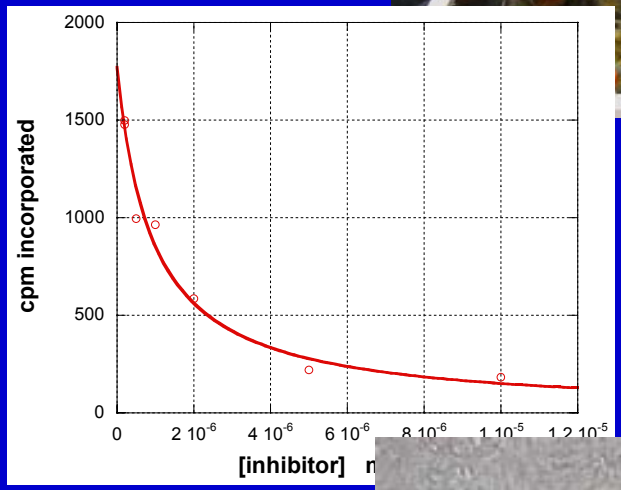
Drug Discovery Pipeline



- Identify molecule(s) which interact with chosen target
- Biological properties attractive/promising but not ideal
- Amenable to analog production

Lead Generation

- Need reliable and accurate biological assays
  - Routine production of target protein
  - Primary biochemical assay
  - Primary antiviral assay
  - Secondary assays (counterscreens)



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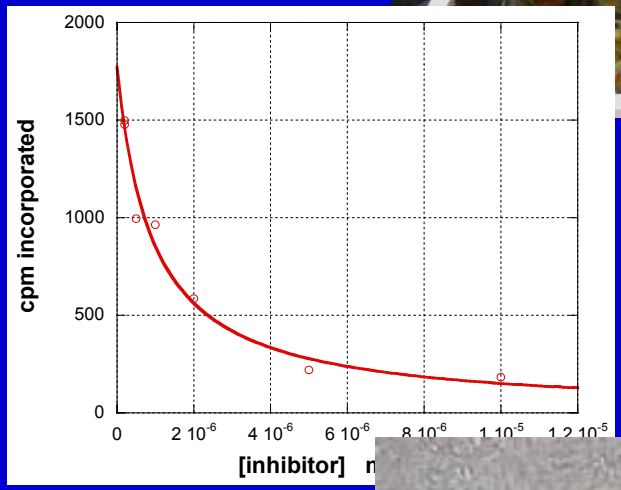
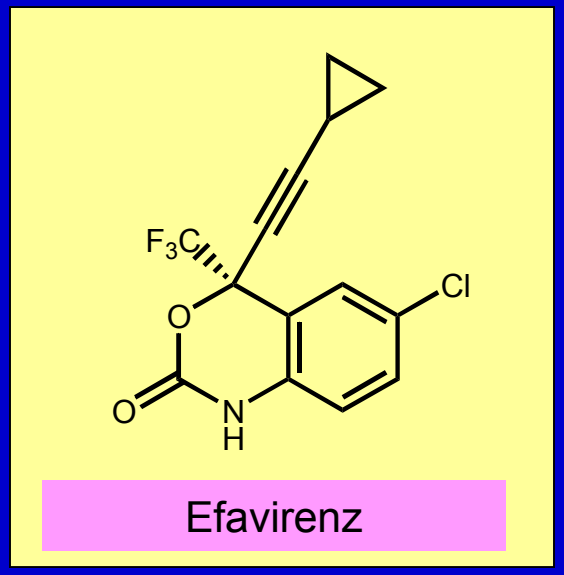
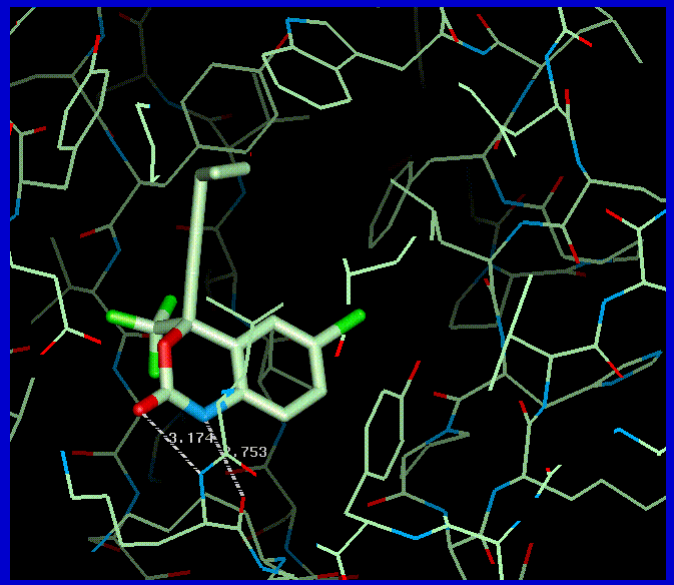


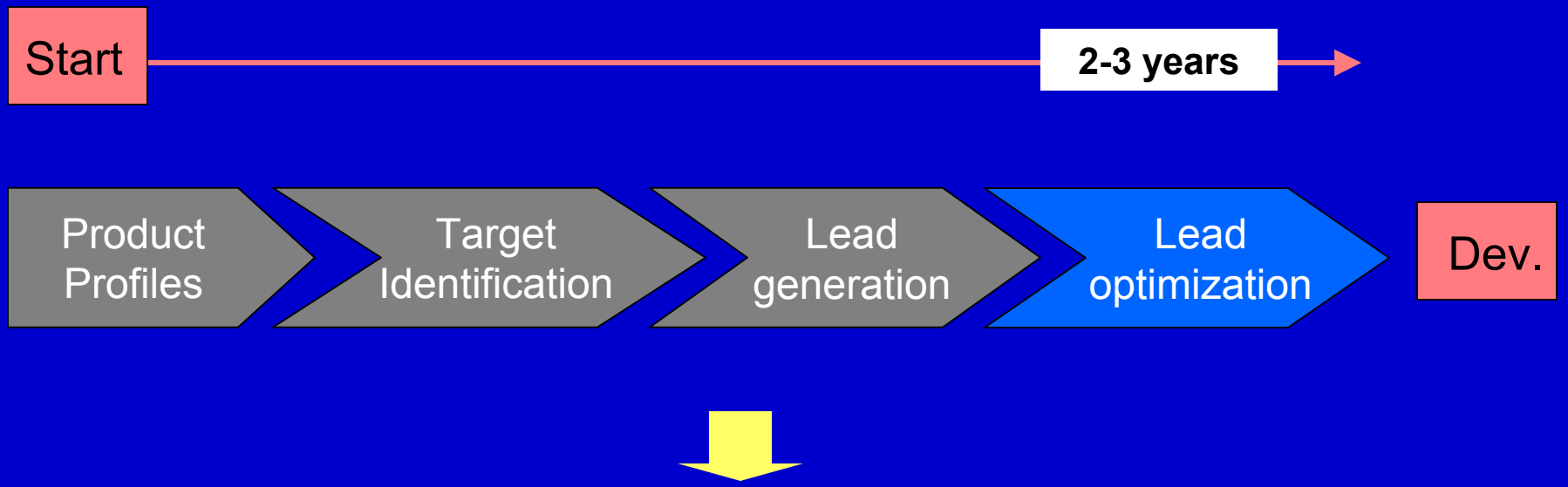
Lead Generation

- High-throughput screening
  - Allows for chance discovery of novel inhibitors
- Example: HIV RT non-nucleoside inhibitors
  - Bind to allosteric site on enzyme surface
  - Disrupt enzyme structure/function





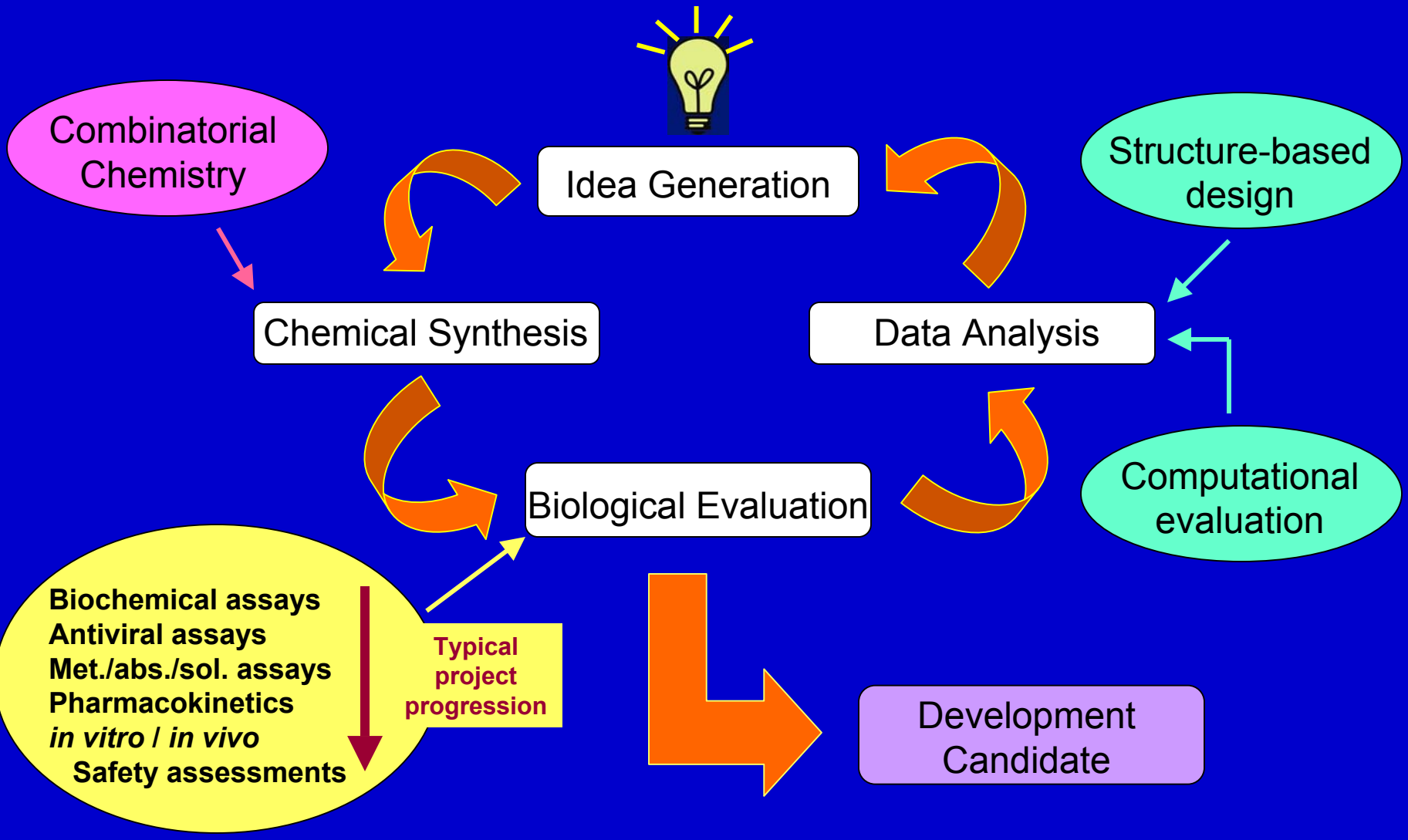
Drug Discovery Pipeline



- Prepare/synthesize analogs of leads
- Improve biological properties
- Optimized compound(s) suitable for clinical development

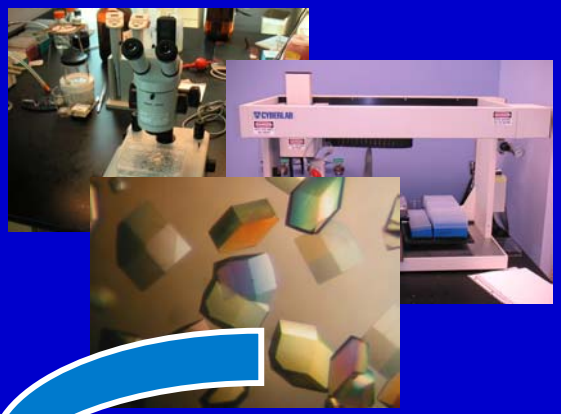
Lead Optimization

- Iterative process impacted by technology

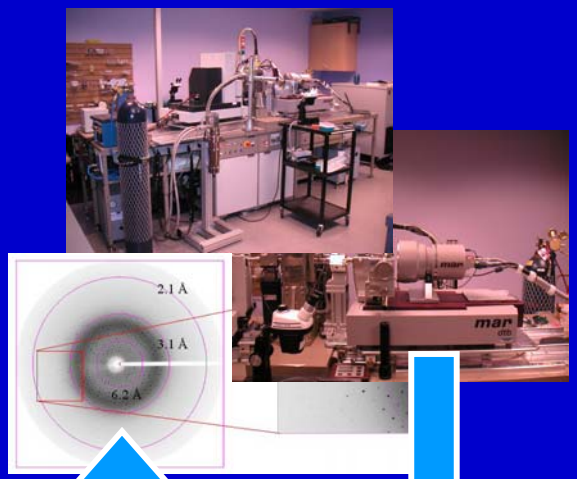


Crystallography Process

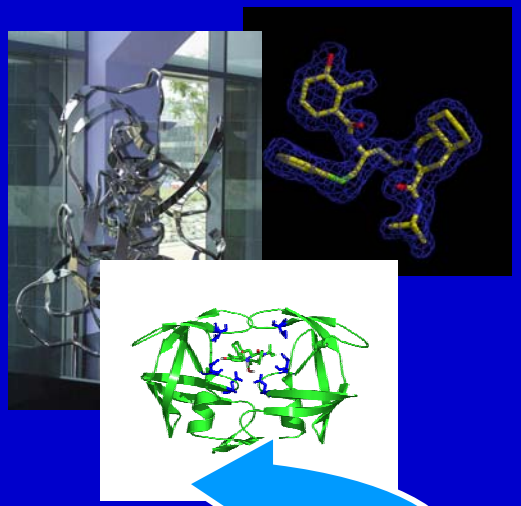
1) Crystallization



3) Diffraction and Data Collection



5) Structure Solution

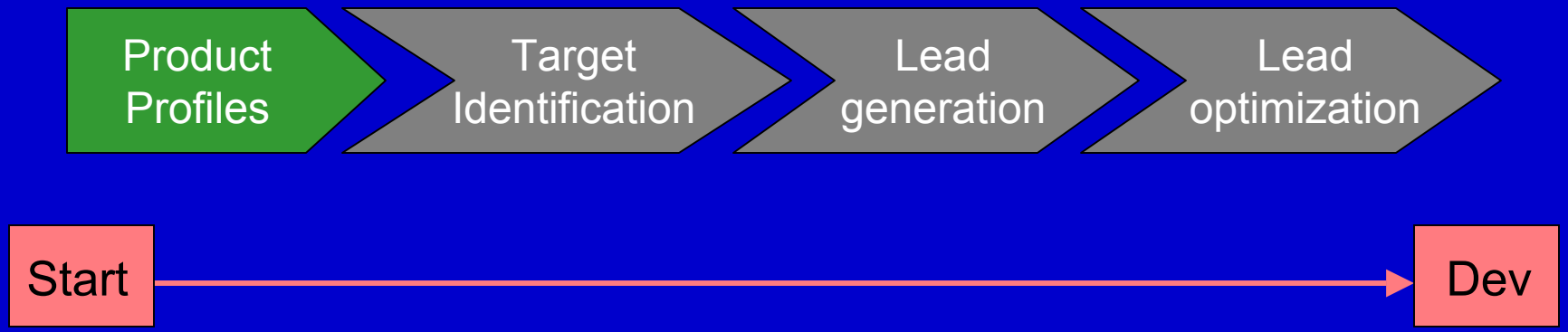


2) Crystal Mounting

4) Data Processing

Future AV Discovery Needs

- Continued understanding of patient and physician needs



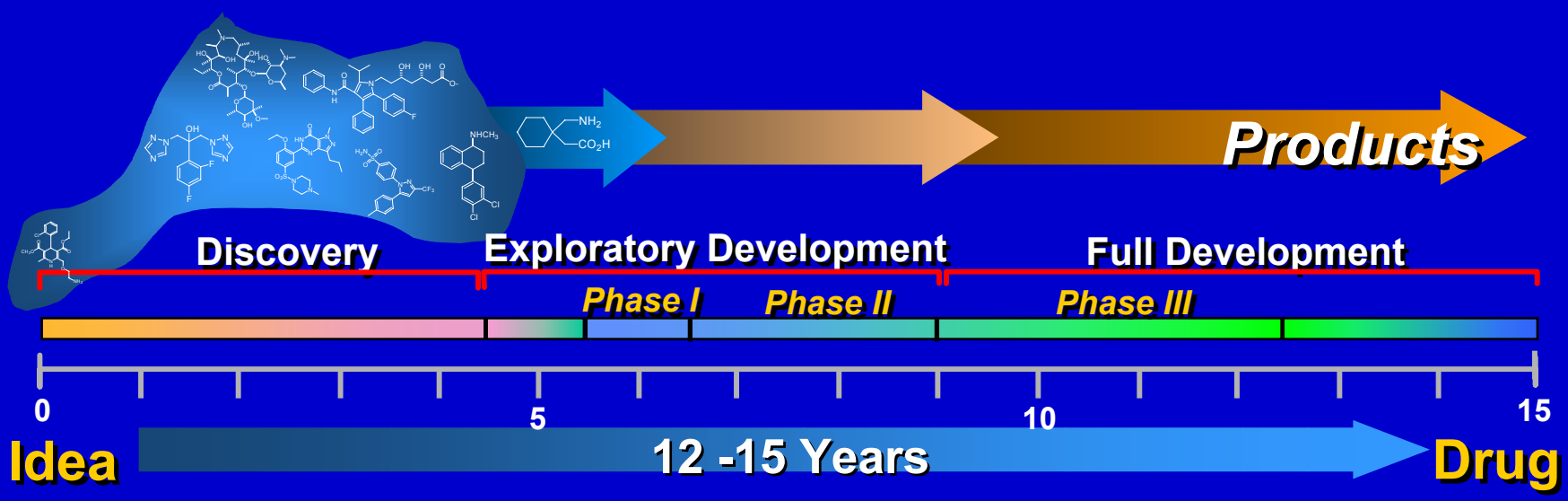
Future AV Discovery Needs

- Improvements in drug discovery/development processes
  - Shorten timelines
  - Reduce attrition

Lead optimization cycle times

Safety predictions

Clinical development times



HIV Drug Discovery

Specific Challenges

RT Inhibitors
(unmet needs)

Nucleosides/Nucleotides

- **Activity against resistant strains (SPD 754)**
- **Lower toxicities**

Non-Nucleosides

- **Activity against resistant strains (TMC 125, Capravirine …)**

Protease Inhibitors
(unmet needs)

- **Activity against resistant strains (Tipranivir, TMC 114, AG1859)**
- **Improve drug levels without toxicities**
  - **(cyp3A inhibitors)**
- **Reduce toxicities**
- **Reduce pill count, dosing frequency**

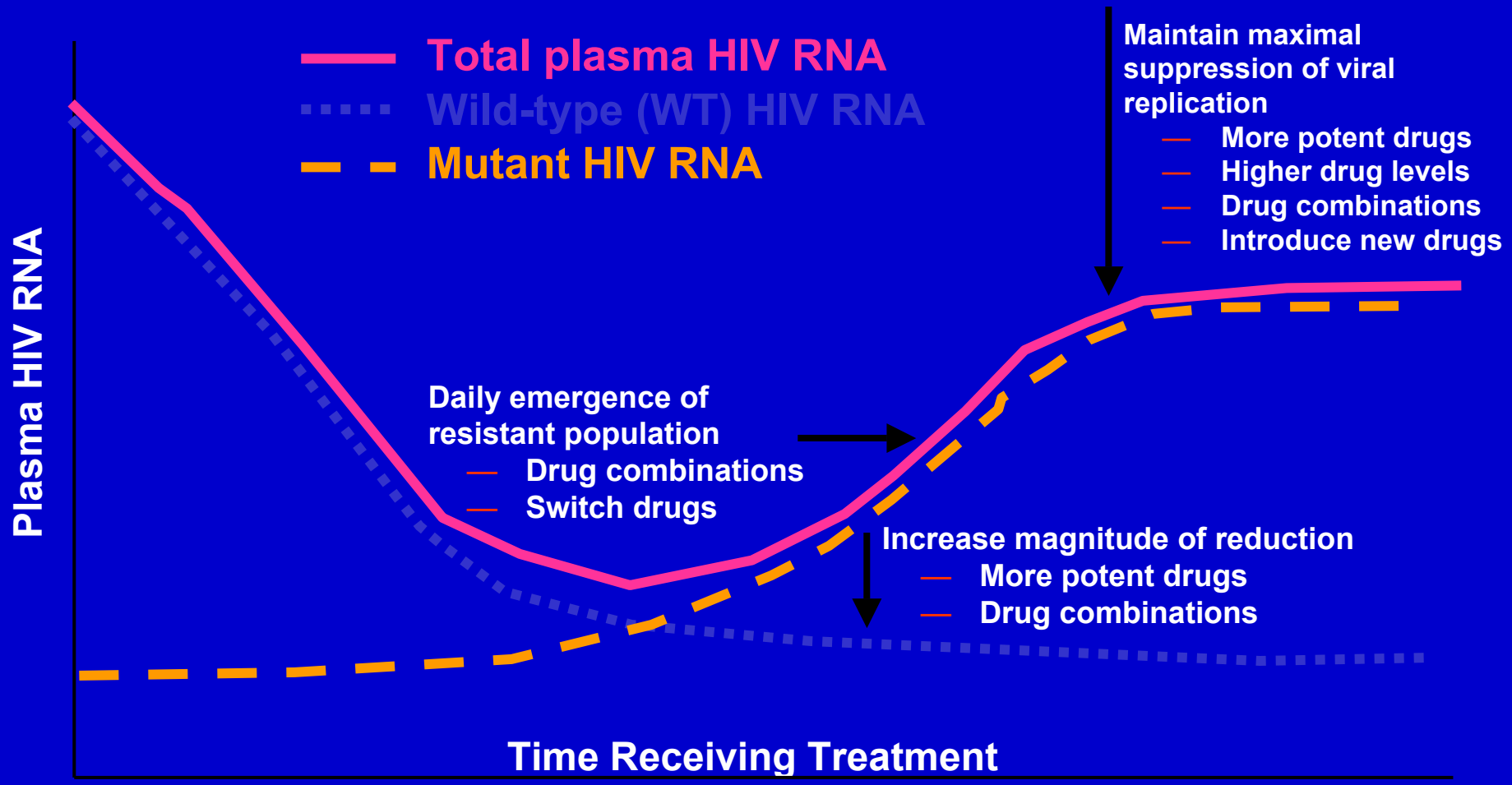
Entry Inhibitors
(unmet needs)

- **Oral bioavailability (UK 427,857, Sch D, BMS 488043)**
- **Cost**
- **New molecular targets (above)**
- **Active against resistant strains (above)**

Treatment Regimens
(unmet needs)

- Simple regimens
- Easily tolerated
- Co-formulated
- Studies in Women and Different Ethnic groups
- Studies in Co-infected Individuals
- Studies in non clade B settings

Strategies to Optimize Antiretroviral Therapy



Havlir. Ann Int Med 1996:124:984.

Resistance

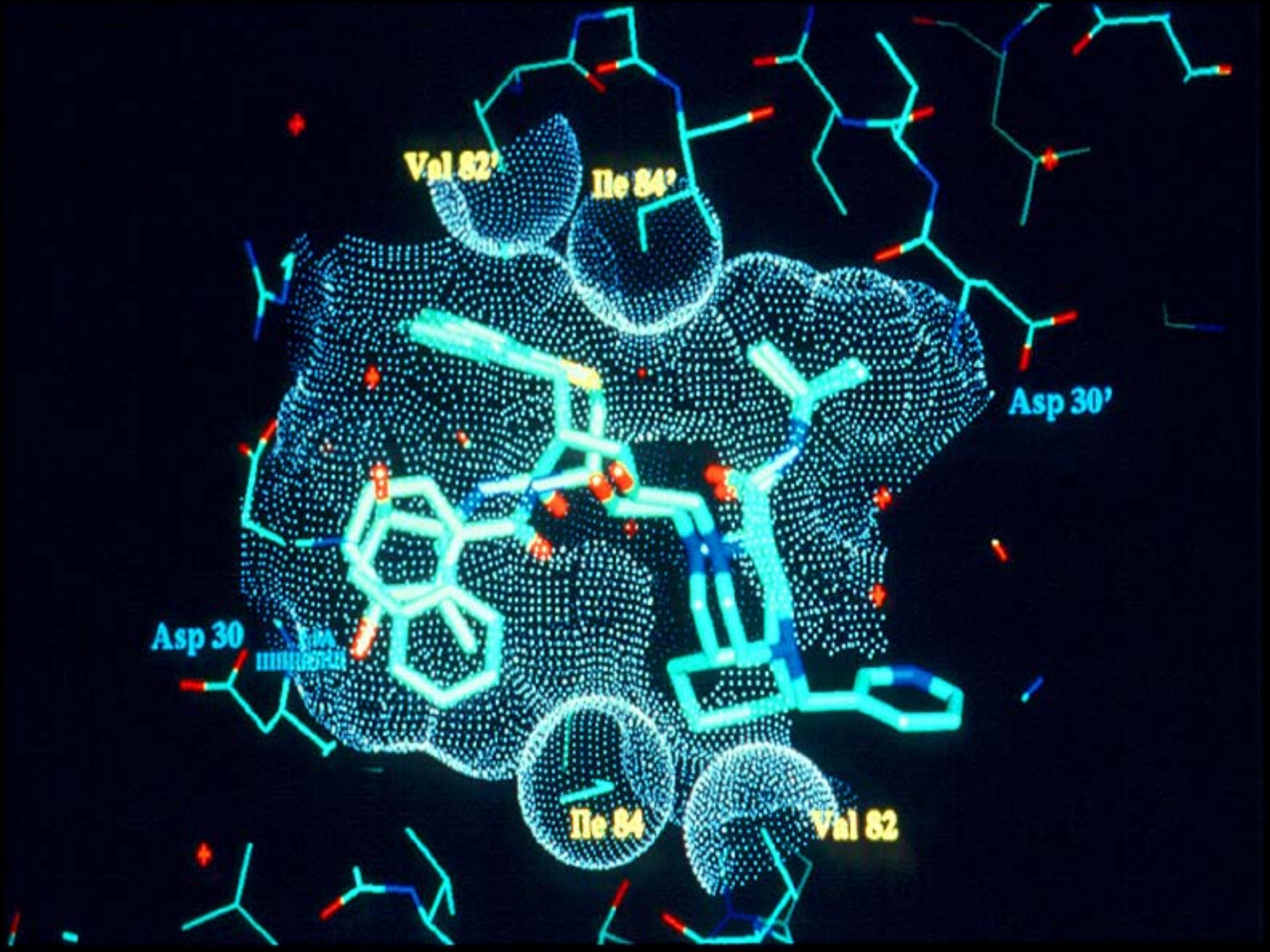
- The selective exclusion of drug as opposed to substrate
- How do they differ – can drug design help discover new MDR active agents?

Drug vs Substrate (PR)

- Drug rigid

- Drug immutable
- Barrier to delivery
- Inactivated by metabolism
- Selective pressure for drug binding is absent
- Insoluble, difficult to formulate

- Substrate flexible – adapts to new binding site
- Substrate can mutate
- In right place at right time
- Not
- Evolved for transition state binding
- Hydrophobic, generated in situ


Val 82'
Ile 84'
Asp 30'
Asp 30
Ile 84
Val 82

Challenges in Discovery
(continued)

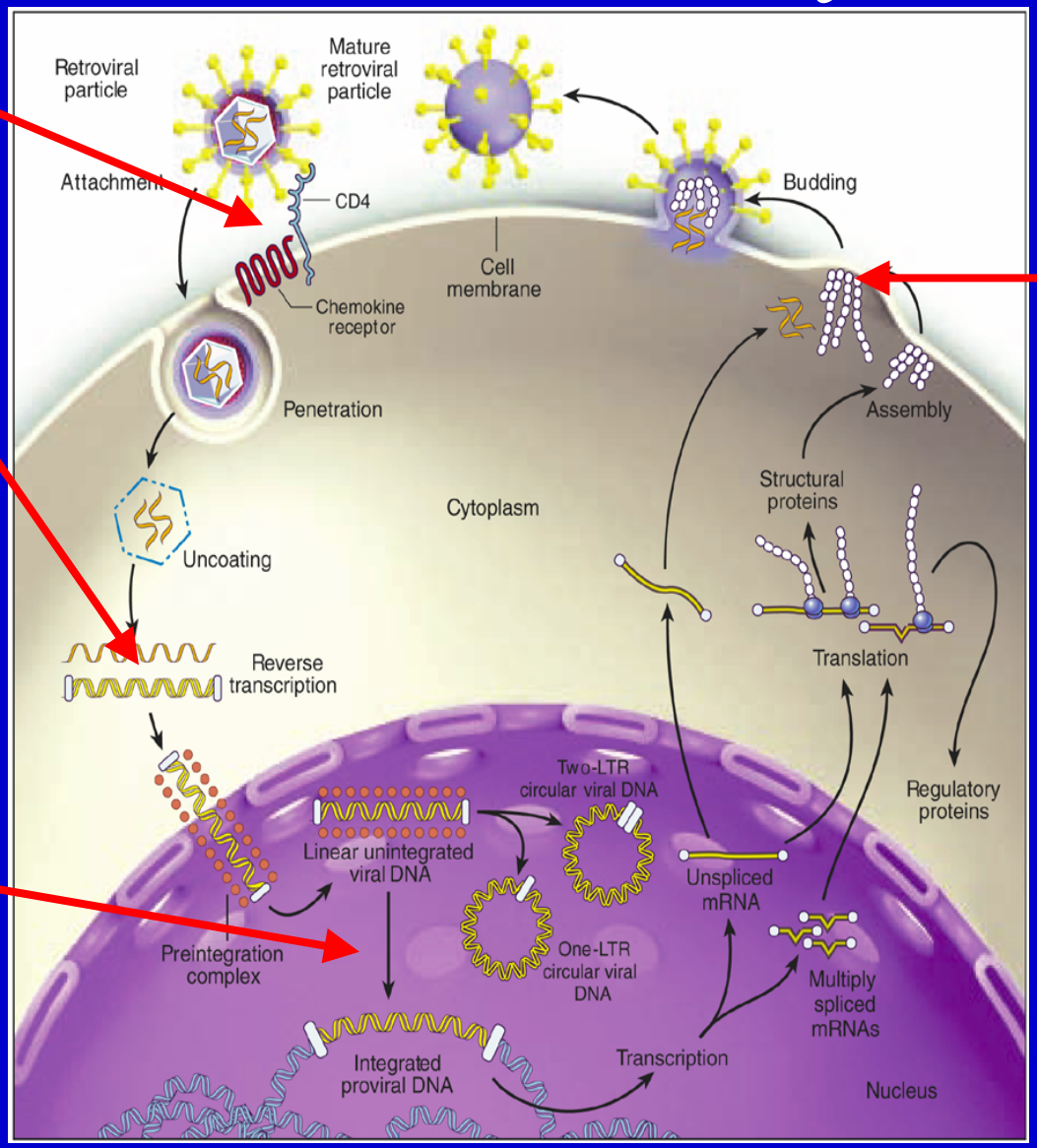
- Safety – in vitro and animal models often inadequate
- Drug interactions – hard to predict in efficacious regimens - often geared to pivotal trial design needs

Retrovirus Life Cycle

Entry inhibitors
e.g. T-20,
UK 427,857
BMS 488043
Sch D

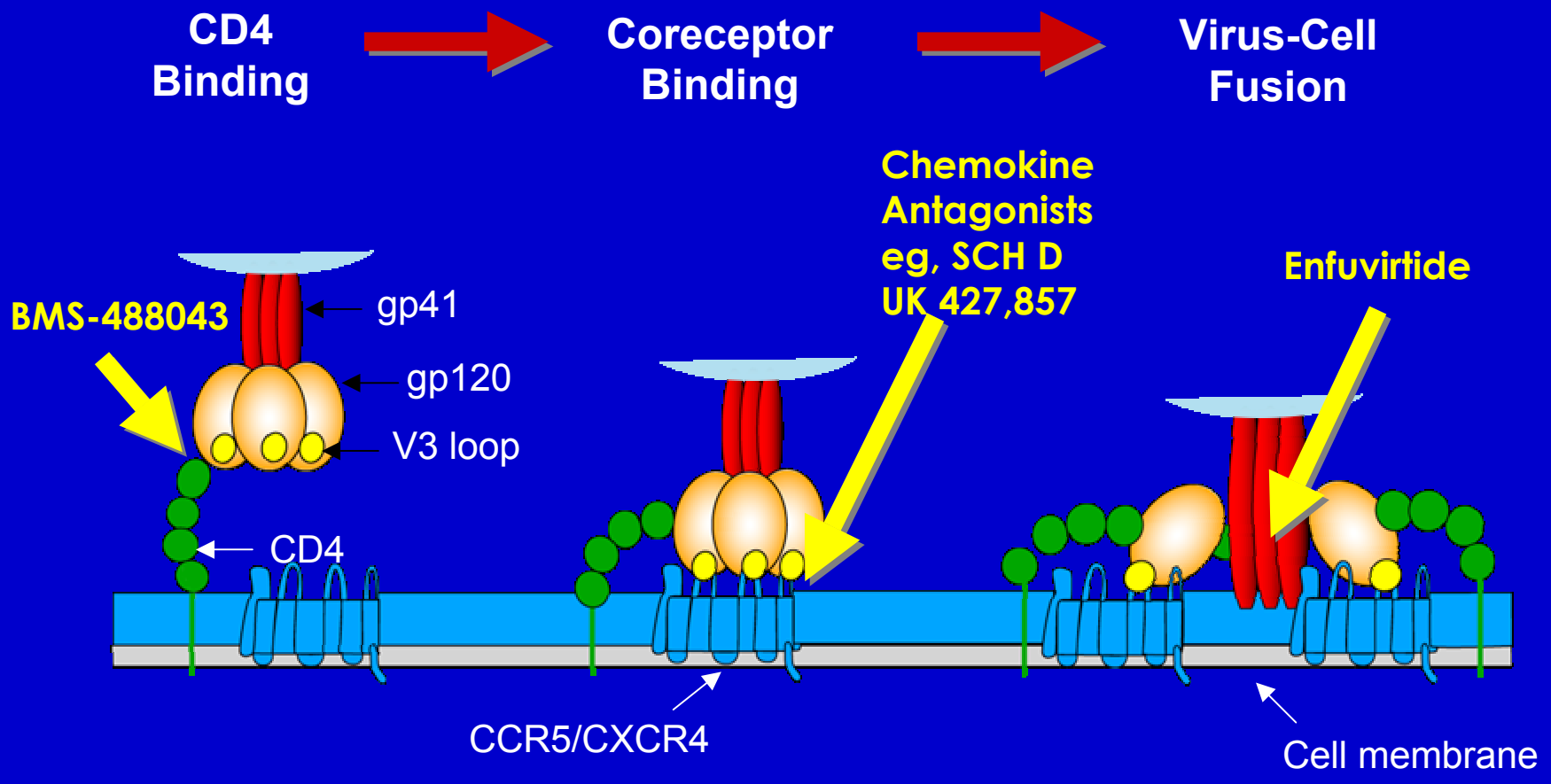
RT inhibitors
ZDV **NVP**
ddI **DLV**
ddC **EFV**
d4T **Capravirine**
3TC **TMC 125**
ABC
TFV

IN inhibitors
L-841,411



PR inhibitors
SQV
IDV
RTV
NFV
APV
LPV
ATZ
Tipranavir
AG1859
TMC 114

HIV attachment and fusion: Targets for inhibition



Future Challenges for Industry

- Collaborate on MDR trials and expanded access
- Collaborate on fixed drug combinations
- Collaborate in the MDR setting and the developing world setting