

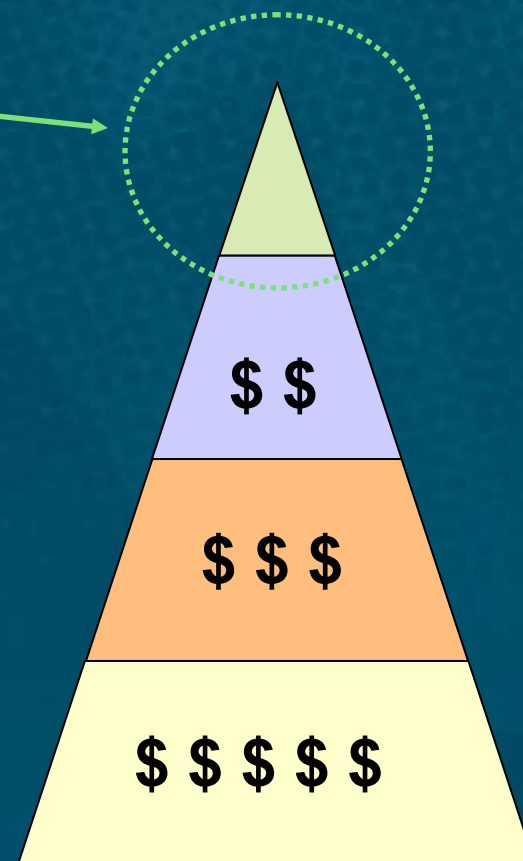
# Filling the Gap: Phenotypic screen, TI/TV or both?

MSF, New York, January 12<sup>th</sup> 2007

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Tibotec NV

# TB Drug Discovery and Development

1. Identify interesting compounds
2. Optimize Lead Compounds  
(chemistry + pharmacology)  
(SAR + ADME)
3. Preclinical development  
(MOA + Toxicity + Pharmaceutical)
4. Clinical development
5. Adoption in regimen



# Global TB Drug Portfolio September 2005

<i>Discovery</i>		<i>Preclinical</i>	<i>Clinical Testing</i>
Carboxylates TB Alliance, Wellesley College	Nitrofuranylamides NIAID, University of Tennessee	Diamine SQ-109 Sequella Inc.	Diarylquinoline TMC207 Johnson & Johnson
Picolinamide Imidazoles NIAID, TACF)	Nitroimidazole Analogs NIAID, Novartis Institute for Tropical Diseases, TB Alliance	Dipiperidines (SQ-609) Sequella Inc.	Nitroimidazole PA-824 Chiron Corporation, TB Alliance
Dihydroliipoamide Acyltransferase Inhibitors Cornell University, NIAID	Thiolactomycin Analogs NIAID, NIH	Nitroimidazo-oxazole Back-up Otsukai	Nitroimidazo-oxazole OPC-67683 Otsuka
Methyltransferase Inhibitors Anacor Pharmaceuticals	Pleuromutilins GlaxoSmithKline, TB Alliance	Synthase Inhibitor FAS20013 FASgen Inc.	Pyrrole LL-3858 Lupin Limited
InhA Inhibitors GlaxoSmithKline, TB Alliance	Isocitrate Lyase Inhibitors (ICL) GlaxoSmithKline, TB Alliance	Translocase I Inhibitors Sequella Inc., Sankyo	Gatifloxacin OFLOTUB Consortium, Lupin, NIAID TBRU, Tuberculosis Research Centre, WHO TDR
Macrolides TB Alliance, University of Illinois at Chicago	Quinolones KRICT/ Yonsei University, NIAID, TACF, TB Alliance	Non-Fluorinated Quinolone TaiGen	Moxifloxacin Bayer Pharmaceuticals, CDC TBTC, Johns Hopkins University, NIAID TBRU, TB Alliance
Cell Wall Inhibitors Colorado State University, NIAID	Screening and Target Identification AstraZeneca		
Natural Products Exploration BIOTEC, California State University, ITR, NIAID, TACF, University of Auckland	Novel Antibiotic Class GlaxoSmithKline, TB Alliance		

**Whole cell screen strategy = green**  
**TI/TV strategy = light blue**

## Phenotypic screen, TI/TV or both?

Target → Drug

Drug → Target

TI/TV identifies *potential* targets

A *potential* target becomes a *validated* target  
..... when a drug has been found against it

The drug validates that the target is “*drugable*”

Why then screen for potential targets first ?

**Disease**

# *The TI/TV Rational Approach*

Pathogenesis  
Comp. genomics  
Proteomics  
Translational research  
Genetic tools  
Molecular Biology

Drug design

Validated target

Phenotypic test  
MIC

X ray

Specificity of hits?

Target identification

Gene cloning & expression

HTS

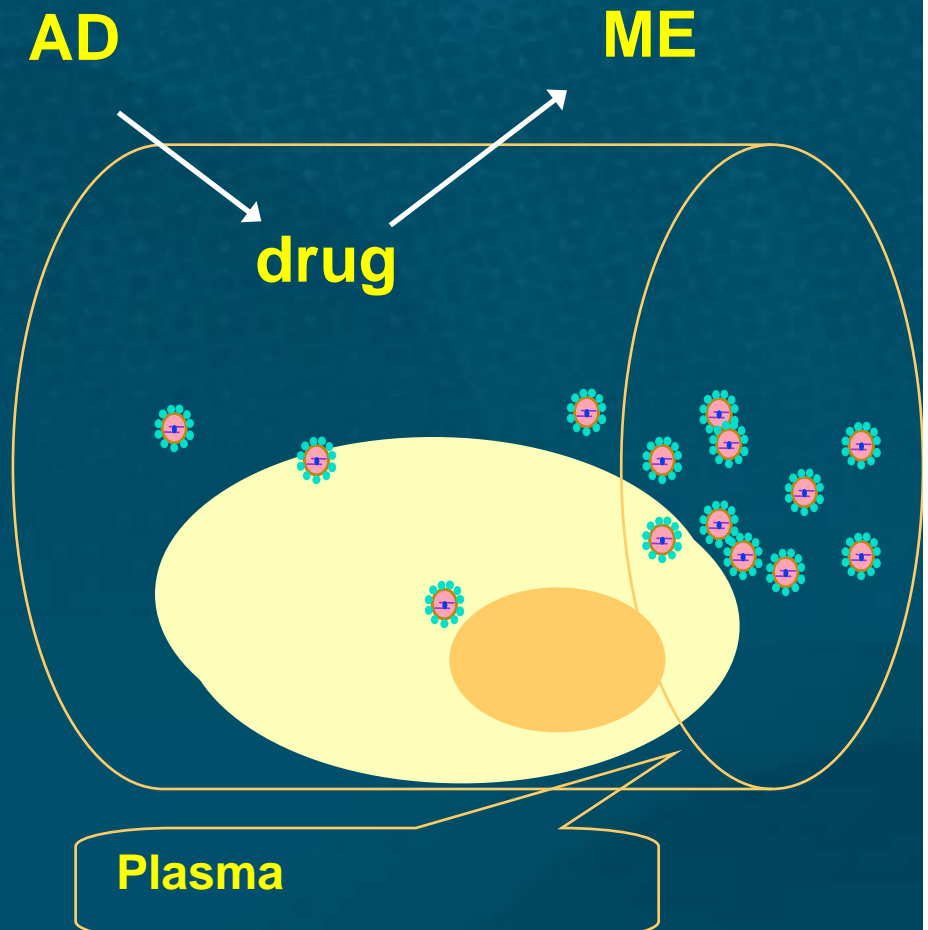
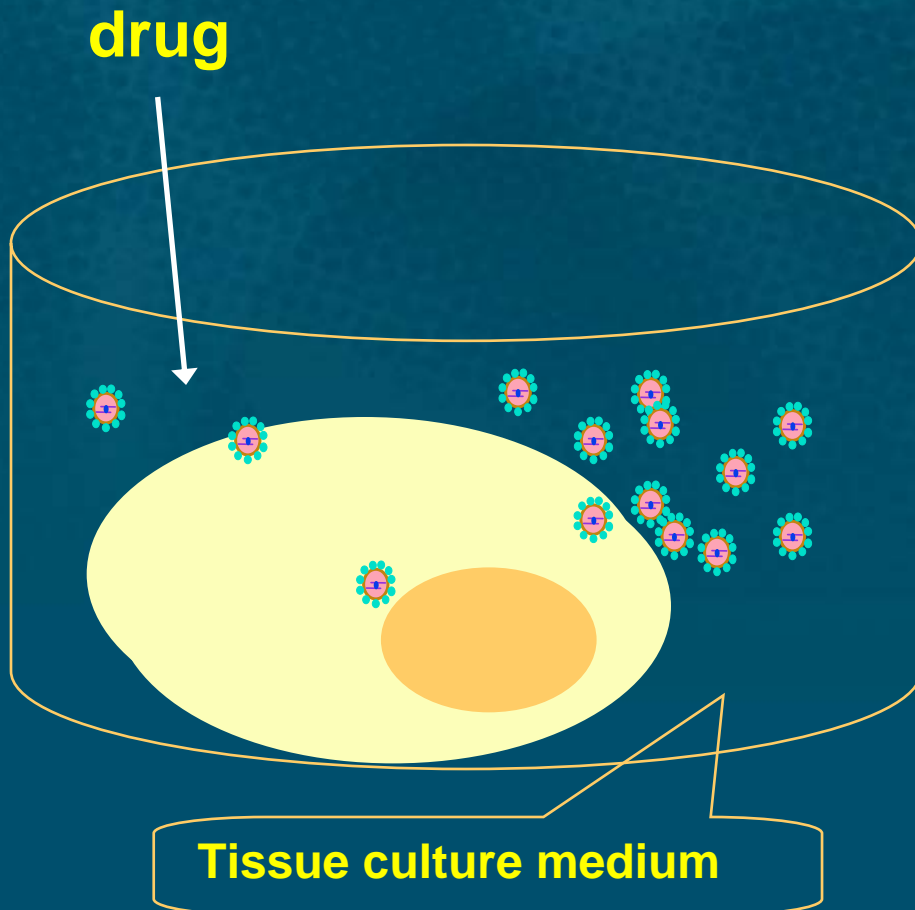
Test 100,000 compounds

time per target ?

# The Phenotypic Screening Approach for antivirals

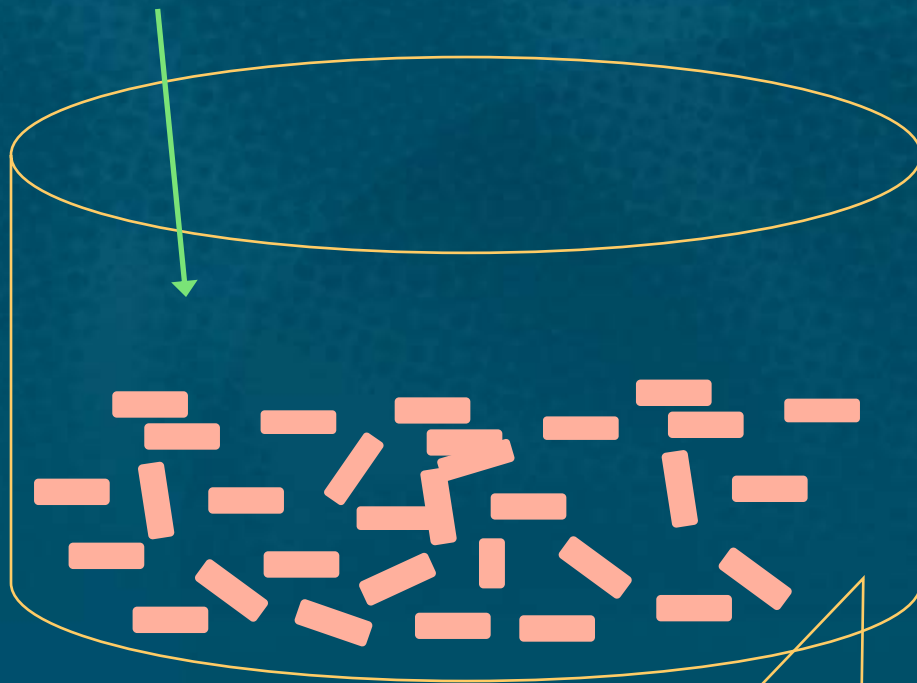
When it works *in vitro*...

it will *probably* work *in vivo* !!



# *The Phenotypic Screening Approach for antibacterials*

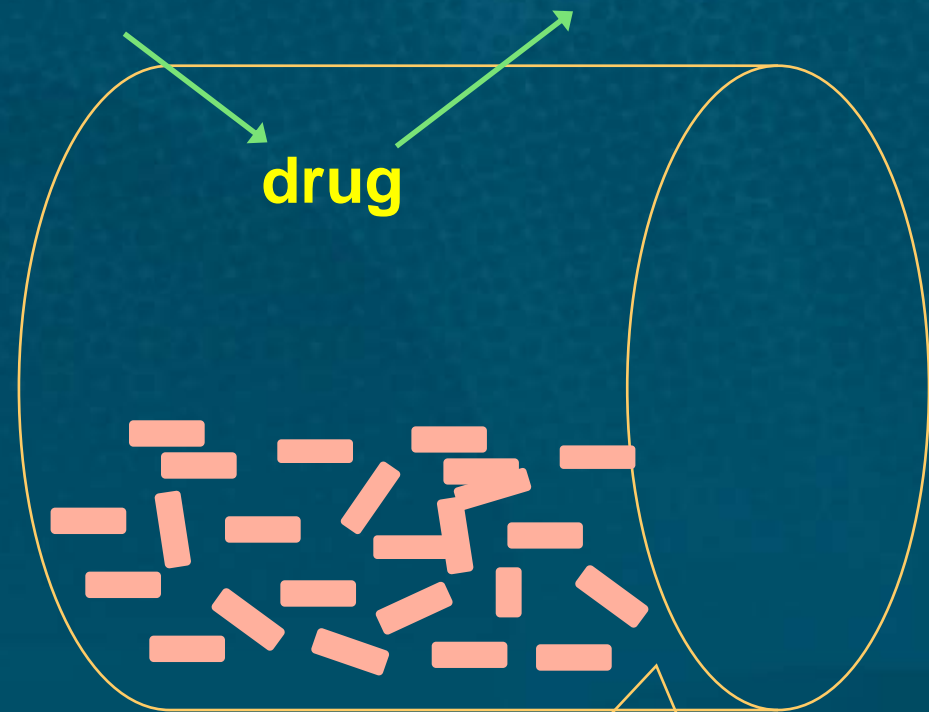
drug



7H9 broth +/-  
specific conditions  
Non-replicating..

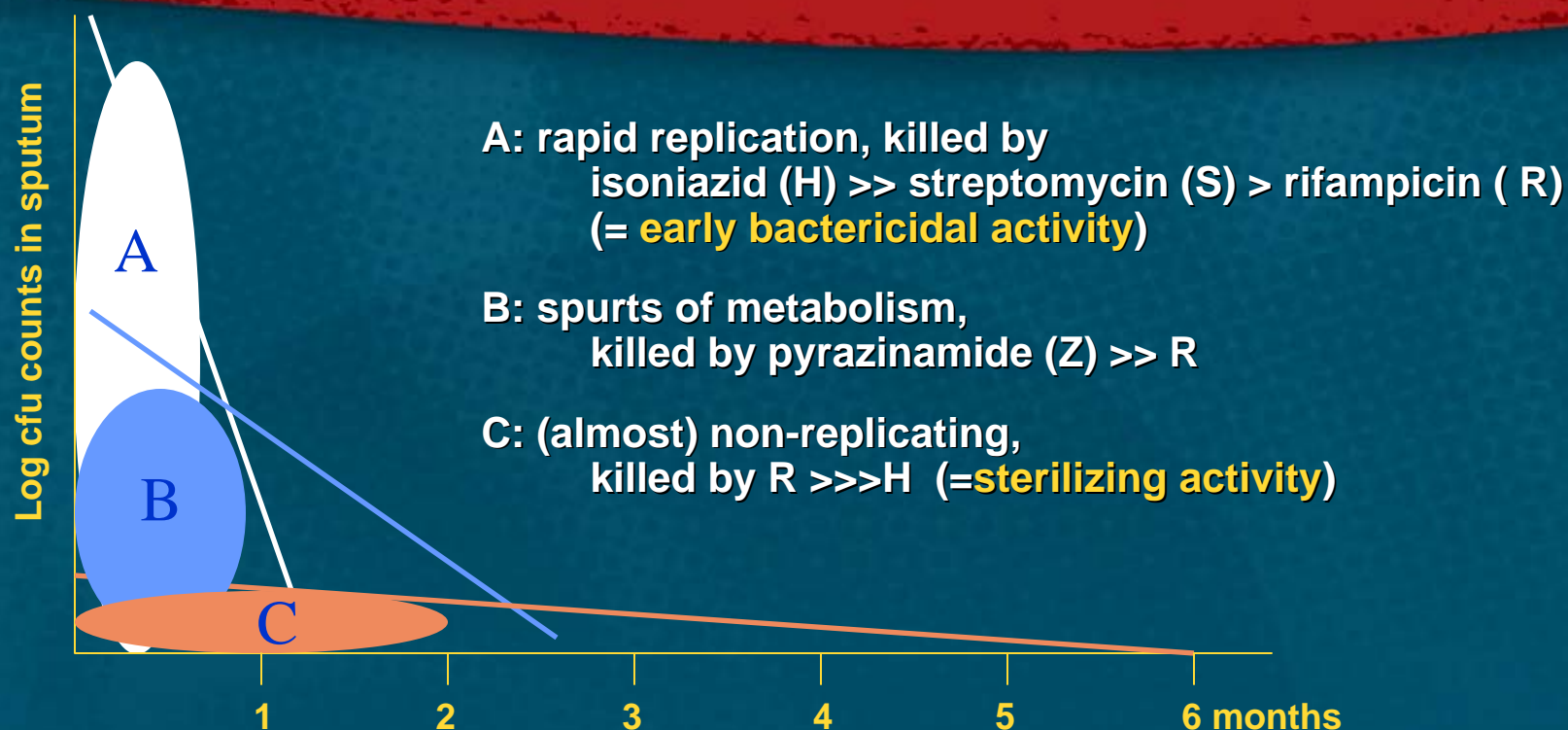
AD

ME



Sputum

# !! Need activity against non-replicating bacilli



Metabolically distinct TB populations explain differences in sensitivities to drugs.  
Shortening treatment duration is entirely dependent on sterilizing activity

**BUT:** As far as we know, most drugs are active against replicating and non-replicating bacilli (exception 1: cell wall synthesis inhibitors / exception 2: pyrazinamide)

**Clinical development of a drug which is not active on replicating bacilli??**



# Discovery Strategies

This is why whole cell screen is so much more efficient!

## TI/TV

- One target per test, but HTS
- Drugability of target unknown upfront
- Regulatory genes not assessed
- Complex targets not assessed
- Prodrugs are inactive
- Compounds that do not penetrate cell membrane not excluded
- Genes essential in vivo ?
- MOA known
- Drug design may be possible

- Identifies R, E, M but not H, Et, J, Z
- Time to test 100,000 compounds against 614 targets ??

## Phenotypic screen

- 614 targets per test but MTS
- Only drugable targets assessed
- Complex targets assessed
- Prodrugs are active
- Compounds that do not penetrate cell membrane are excluded
- Specificity of activity easier to assess
- Genes essential in vivo not assessed
- MOA unknown upfront
- No drug design

- Identifies R, E, M, H, Et, J but not Z
- Time to test 100,000 compounds against all targets = 1-2 years

# The most efficient way to fill the gap ?

The most *rational* way is perhaps not the most *efficient* way...

The most efficient way to fill the gap ?

$$\text{Efficiency} = C \times T \times L$$

Number and Diversity  
of **Compounds** tested

x

Number and diversity  
of **Targets** tested

x

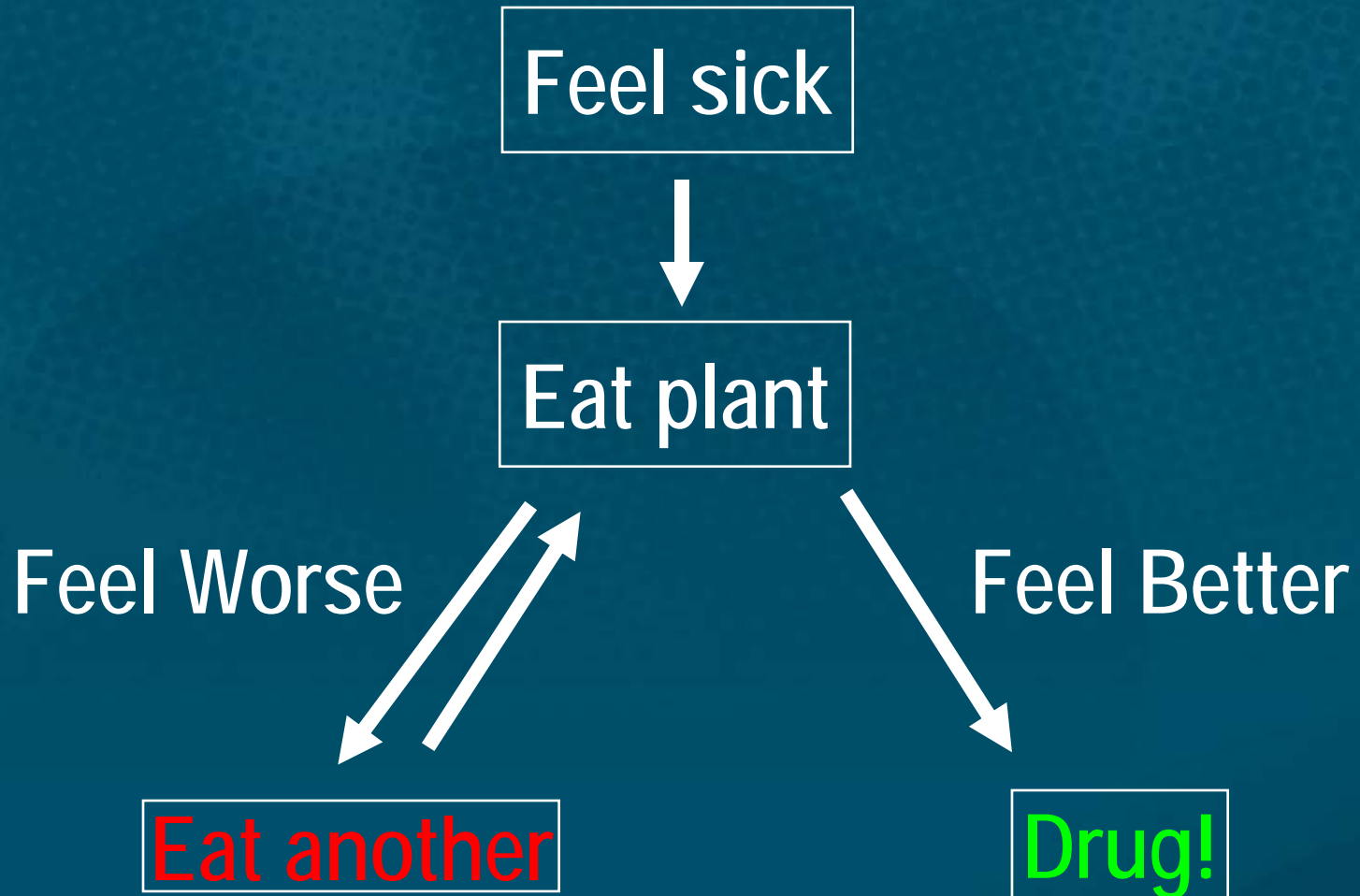
**Luck** factor

Start with testing  
all marketed drugs!!

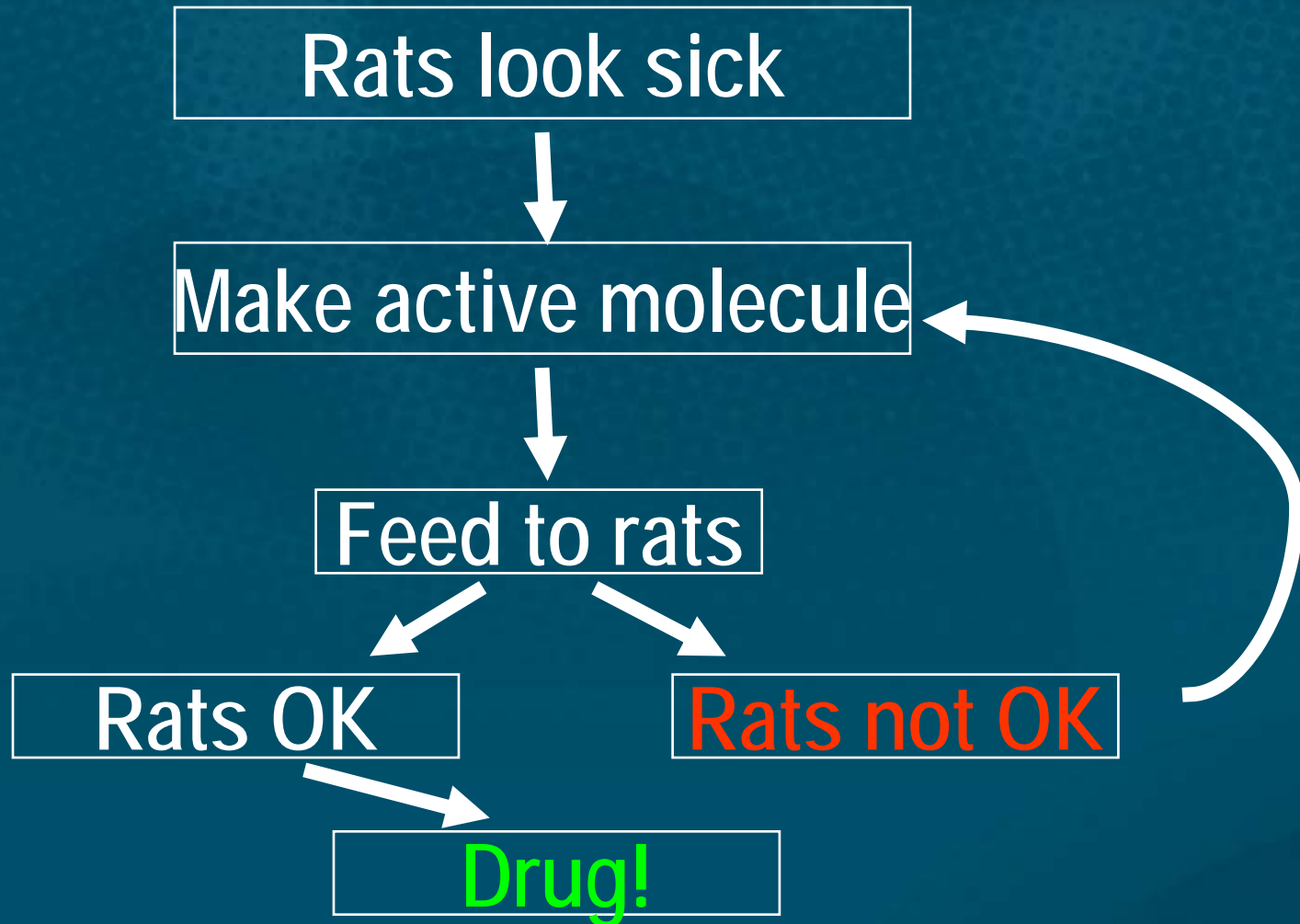
Phenotypic screen  
and TI/TV  
...in that order!

**Backup slides**

# Drug Discovery: The Early Days



# Drug Discovery: The Golden Age



# Drug Discovery in the 21st Century



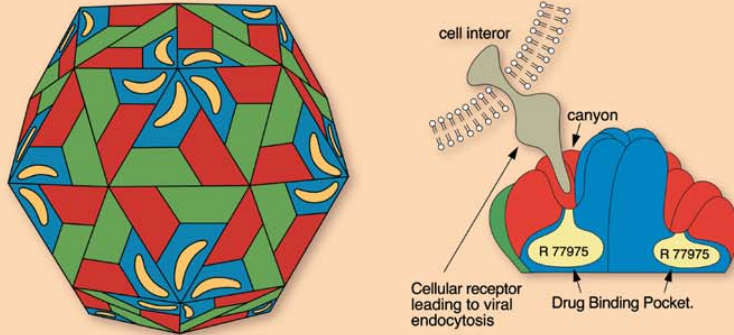
# Access to libraries

- Need to select **drug-like** compounds
  - Need chemical **diversity**, more important than numbers
  - Chemical library is the most precious asset of a company
  - Many compounds available in very limited amounts
  - Unlikely to get external access to libraries
- 
- Convince companies to start in-house whole cell screening
  - 2-3 FTE's is all what is needed
  - BSL-2 facility can be used for apathogenic mycobacteria
  - IP for non-TB applications remains in company
  - IP for new analogues of lead compounds needs to be discussed

# Discovery of Antimicrobial Agents and their targets

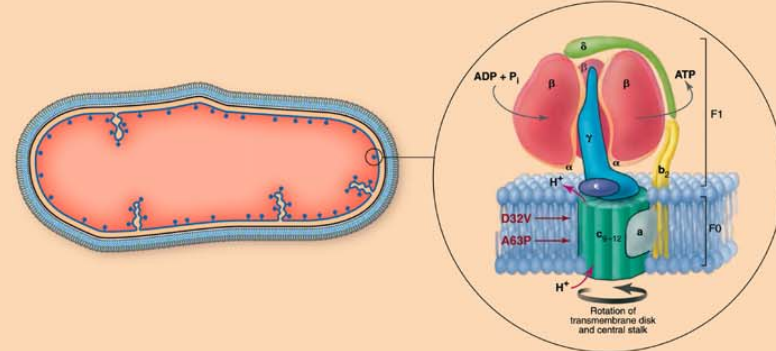
R 77975 inhibits viral uncoating of Human Rhinovirus (MIC= 30 nM)

*Andries et al., 1992, AAC, 36, 100-107*



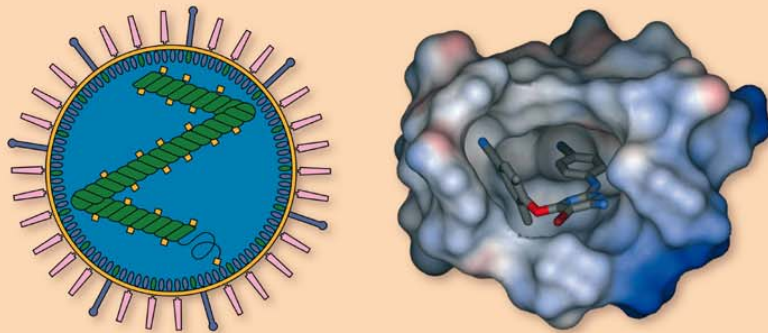
R 207910 inhibits ATP synthase of *Mycobacterium tuberculosis* (MIC= 30 nM)

*Andries et al., 2005, Science, 307, 223-227*



R 170591 inhibits viral fusion of Respiratory Syncytial Virus (MIC= 30 nM)

*Andries et al., 2003, AVR, 60, 209-219*



R 165335 inhibits Reverse Transcriptase of Human Immunodeficiency Virus (MIC= 1.0 nM)

*Andries et al., 2004, AAC, 48, 4680-4686*

