# Focusing projects with Target Product Profiles (TPPs) and Target Candidate Profiles (TCPs)

Worked Example:  ASAP SARS-CoV-2/MERS-CoV Mpro program

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# Agenda



- What's a TPP and a TCP?
- Why MERS&SARS?
  - Our approach to TPPs and TCPs - ways of working
  - What did we learn from SARS2
- MERS&SARS  TPP - work through
- MERS&SARS TCP - work through
- Call for feedback

# TPPs and TCPs



- **TPP**:- Target Product Profile
  - properties of the ***product*** – irrespective of biological Mode of Action
  - key part of an investigator's brochure, and in the end the product label

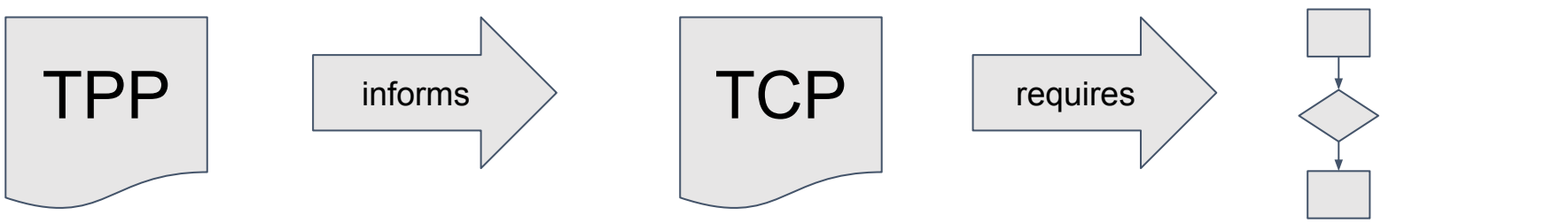
*The concept of a target product profile is not special to drug discovery, used across many industries to focus design teams on delivering to the client(patient and clinician) needs*

- **TCP:-** Target Candidate Profile
  - what ***features of a molecule*** are needed to deliver a TPP via a particular Mode of Action

- Many TCPs may deliver to the same TPP

- For examples see

Burrows, et al, New Developments in Anti-Malarial Target Candidate and Product Profiles. Malaria Journal 2017, 16 (1), 26. https://doi.org/10.1186/s12936-016-1675-x.



# Why MERS&SARS?: HCoV Summary



| | Class | | 1st Isolation | Case Fatality Rate |
|---|---|---|---|---|
| 229E | α-CoV | Duvinacovirus | 1966 | - |
| OC43 | β-CoV lineage A | Embecovirus | 1967 | - |
| SARS-CoV | β-CoV lineage B. | Sarbecovirus | 2002 | 9.6% |
| NL63 | α-CoV | Setracovirus | 2004 | - |
| HKU1 | β-CoV lineage A | Embecovirus | 2004 | - |
| MERS-CoV | β-CoV lineage C | Merbecovirus | 2012 | 34.4% |
| SARS-CoV-2 | β-CoV lineage B | Sarbecovirus | 2019 | 3.5% |

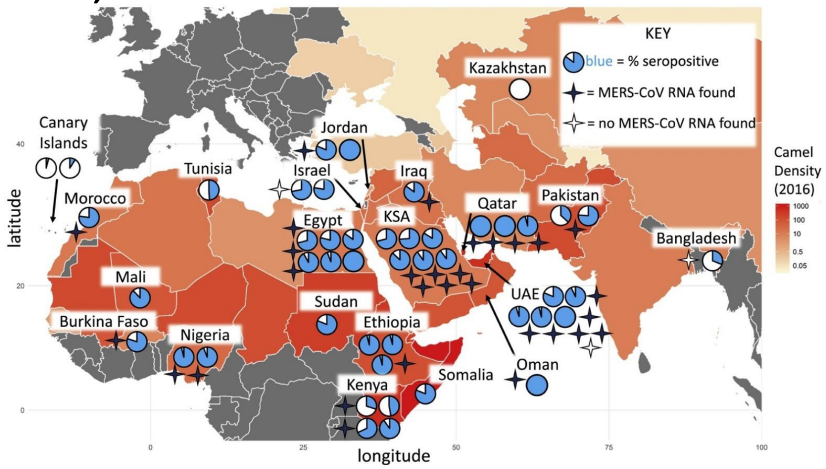
- Ye at al Int J Biol Sci. 2020 Mar 15;16(10):1686–97.

# Anti-MERS-2: Rationale



- MERS is endemic in dromedary camels,[1] & climate change is increasing camel population [2]
- With both SARS-COV2 and MERS endemic in high population LMICs (Egypt, Nigeria, Pakistan total population = 0.5Bn), the opportunity for a recombination event is high and the risk should be mitigated.[3]
- MERS is an airborne respiratory virus,[4]
- Current MPro inhibitors have MERS as a weak point, other (tested) coronaviridae show broadly equivalent potency with current series,
- A MERS type lineage C β-CoV would not be treatable by existing agents,

→ high pandemic risk



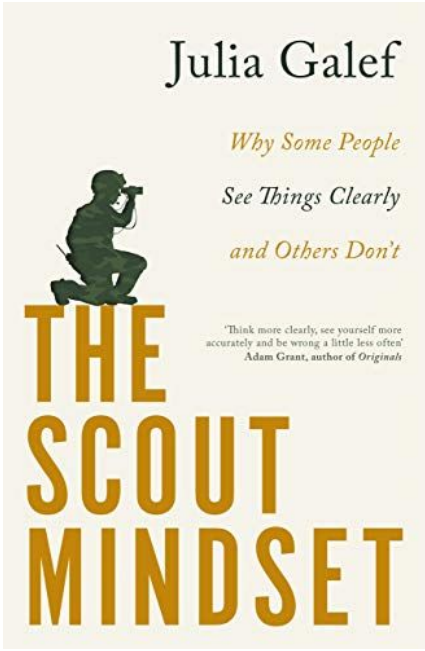

(1) Epidemics. 2019 Dec 1;29:100350.
(2) https://www.bbc.com/future/article/20210122-the-coronavirus-10-times-more-deadly-than-covid
(3) Supplementary recommendations for the epidemiological investigation of SARS-CoV-2 in exposed animals Rome, Italy: FAO; 2021 16 p. https://www.fao.org/documents/card/en/c/cb7141en/
(4) Indoor Air 2018, 28, , 51–63. https://doi.org/10.1111/ina.12430.

# Our approach to TPPs and TCPs



Part of ASAP's ethos is to "draft early and refine"

- "good now and improving" beats "perfect in 6 months"
- kaizen - continuous improvement
- software dev: agile rather than waterfall development
- "Scout mindset"
  - set an initial goal,
  - start progressing,
  - check if the goal is still appropriate,
  - refine goal, (check if complete!)
  - alter course to head for new goal,




All our TPPs and TCP are "*the best we have today, and open for improvement*"

# Learning from SARS2



Another lethal airborne respiratory infection like SARS2:

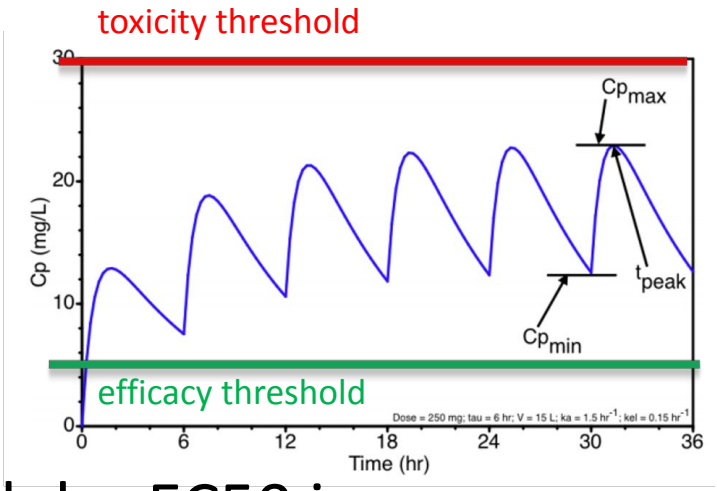
- goal would be to suppress at epidemic level before becoming pandemic,
- would need to be available orally for health worker treatment / protection & “cordon sanitaire” pre-exposure prophylaxis (PrEP)
- wide range of population would need to be able access therapy

- drug safety consequences
  - access by women of childbearing age
    - no carcinogenicity, mutagenicity, teratogenicity
  - geriatric patients and others with co-morbidities = multiple other therapies,
    - avoid drug-drug interactions: especially CYP P450 inhibitors and transporter inhibitors
  - general highly safe therapies to avoid “pandemic panic hesitancy” issues
    - e.g. Molnupiravir concerns, vaccine fertility misinformation

# How to plan for an unknown disease?



Assume that for a **direct acting** anti-viral:




- inhibition of viral replication in multiple model cell lines will generate a relevant EC50
- continuous in vivo **free drug cover** in plasma over the cellular EC50 is a reasonable pharmacodynamic model
  - assuming a relativity well distributed compound where plasma: tissue ratios are reasonable
  - = where the compound can easily access all body compartments and tissues where the virus is replicating
- efficacy in 1 or more animal models of similar disease e.g. MERS as a model for a future hCoV

# TPP – MERS&SARS2 (June 2022 draft)

NON-CONFIDENTIAL

ASAP Accessible Antivirals to Prevent Pandemics

**Name: TPP-1: MERS type respiratory beta coronavirus**

| Property | Minimum Essential | Ideal |
|---|---|---|
| Drug Product | oral | iv with oral step down (prophylactic?) |
| Dosing regimen | tid | uid |
| Pre-clinical efficacy | Efficacy in >= 3 relevant cell models with projected (including primary cell model) 24h cover over EC90 from TID dosing | 3 log drop in viral load in mouse model |
| Transmission blocking | No | Yes |
| Bioavailability / food effect | Predicted >= 30% / fed fasted <3x change | Predicted >= 50% / fed fasted no change |
| Drug-Drug Interactions | No unmanageable risk in terms of solid state or PK interactions | No risks in solid state or PK interactions |
| Safety and Tolerability | Few and manageable drug-related SAEs | No drug-related SAEs; minimal drug-related AEs that do not result in Study exclusion |
| Pregnancy | Not contra-indicated in second or third trimester | Not contra-indicated in 2nd or 3rd trimester, no embryo-fetal toxicity in 1st trimester in preclinical species |
| Shelf life of product | >=2y | >=5y |

Oral is essential for AViDD, iv is imaginable for use in ICU, but not a primary goal, iv & oral is from a medicinal chemistry perspective very hard as they are conflicting goals (especially in a high dose agent)

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Animal model efficacy a reasonable surrogate for an unknown disease, mouse most probable at discovery stage, metabolism issues with hamster, logistics with ferret

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A low bioavailability if not variable would be possible - but would require and extremely potent agent. Fed/fasted is a compliance issue

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PK interactions - is critical with patients on multiple therapies, CYP P450 inhibitors could cause overdosing of other therapeutics with the potential for lethal interactions.

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Serious Adverse events in a new therapeutic would, from the COVID-19 experience, have the potential to critically impede both clinical trials and effective use.

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COVID-19 has demonstrated that potential contraindication in pregnancy is an issue of uptake in HMIC's and as effective contraception is unavailable in many LMICs contraindication in pregnancy becomes contraindication for all women of child bearing age - a critical failure.

# Project 5 : Lead Optimization

## SARS-CoV-2 / MERS-CoV MPro - TCP **Orally bioavailable inhibitor for SARS-CoV-2 and MERS-CoV**

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Enzyme target is dependant on the enzyme→ cell dropoff - unclear until we have enough compounds with a range of potencies - but assume 10x dropoff initially and refine

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The more potent the better - achieving free Cmin > EC90 (CPE) for 24h is easier the better the potency (obviously…)

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Very much a work in progress - significant reduction in measured animal viral load seems a minimal requirement

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MERS appears to be the hardest other CoV to inhibit and with SARS1 is the most pathogenic.

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PK enhancers such as Ritonavir generate DDI's with large numbers of other CYP P450 metabolised drugs

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poor solubility is a risk for poor cellular activity and poor absorption

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Protease panel is the target specific risk factor, non-selective protease inhibitors will generate toxicities that will probably be unacceptable, flag for early inclusion in the test cascade

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CYPs and transporters - DDI critical

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CYPs and transporters - DDI critical

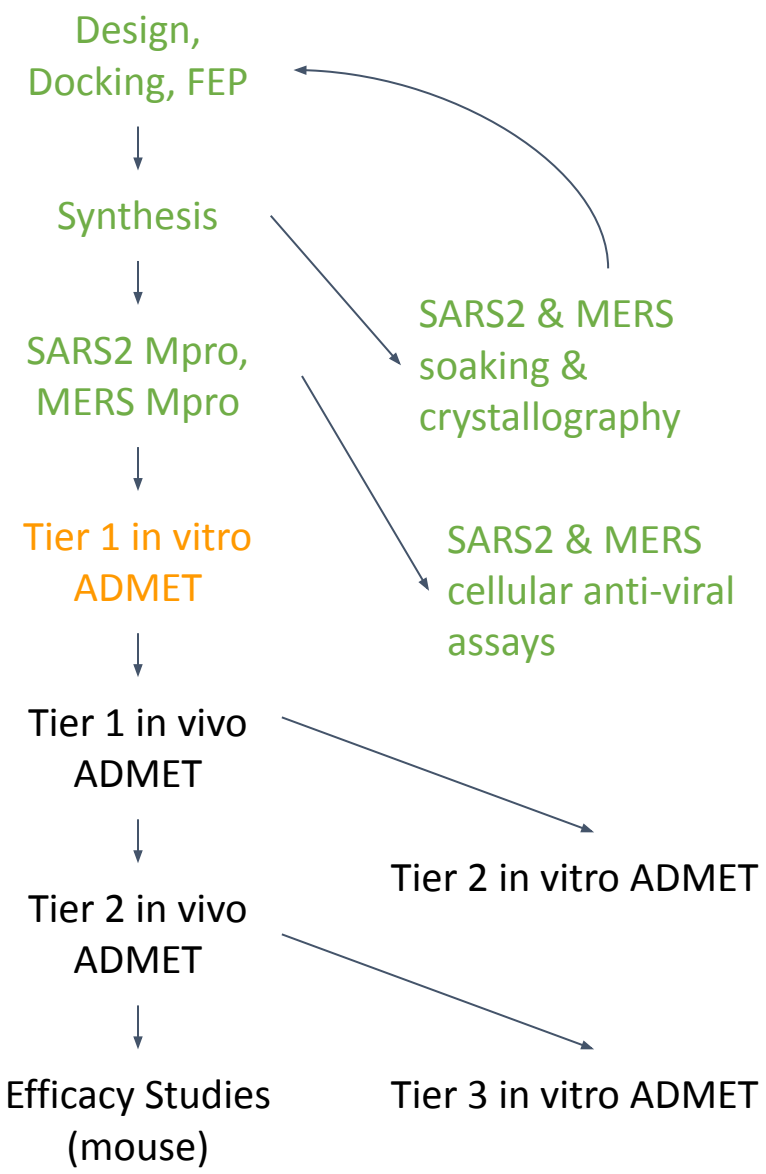
Ames test as 1st test for mutagenicity/ teratogenicity

# ASAP: Lead Optimization

## SARS-CoV-2 / MERS-CoV - Assay Cascade - re-model with series development

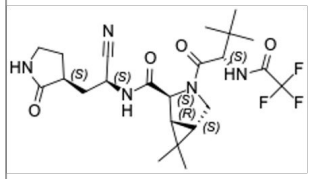
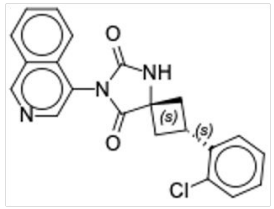
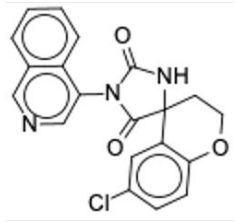
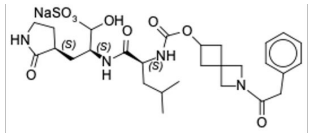
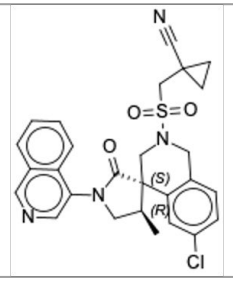
NON-CONFIDENTIAL

| Area | Assays | Entry Criteria |
|---|---|---|
| In Vitro biochemistry | SARS2 Mpro, MERS Mpro | All compounds |
| Cellular assay | SARS2 , MERS | SARS2&MERS MPro IC50 <1uM |
| In vitro ADMET Tier 1 | solubility(kinetic), LogD, mics(hu), mics(mouse)<br>MDCK Permeability , A—>B | SARS2&MERS MPro IC50 <1uM |
| In vitro ADMET Tier 2 | Thermodynamic Solubility, MDCK-MDR1 ER<br>microsome(rat), hepatocyte (mouse, rat, human)<br>Plasma Protein binding (mouse, rat, human, FCS)<br>CYP Inhibition 5 Cyps, Patch clamp hERG, NaV 1.5, CaV 1.2 | critical leads (eg for RLM: heps: bioavailability comparison) + in vivo efficacy candidates |
| In vitro ADMET Tier 3 | 3A4 TDI, PXR induction, BSEP, AMES (2 Strains)<br>Dog: Microsome, Hepatocyte, Plasma Protein – Dog | critical leads + short list |
| In vivo ADMET Tier 1 | mouse iv cassette 5 compounds per cassette | critical leads + rodent mics Clint < 100ml/min/mg & cellular efficacy IC50 < 1uM |
| In vivo ADMET Tier 2 | Formulation studies, Mouse iv, po bioavailability, Rat iv, po & bioavailability, | in vivo efficacy candidates |
| Efficacy studies | Mouse SARS2 and Mouse MERS | expectation of free cover over EC50 for 24h |
| Selectivity / tox screening | Protease panel (61)<br>CEREP in vitro tox panel | critical leads + short list |



# Project 5 : Lead Optimization
## SARS-CoV-2 / MERS-CoV MPro - MERS vs SARS2 background

NON-CONFIDENTIAL

| Structure |  |  |  |  |  |
|---|---|---|---|---|---|
| Identifier | Nirmatrelvir | Carlsson-19 / | VLA-UCB-29506327-1 | Groutas-3c | MIK-ENA-17e27e9c-1 |
| SARS2 MPro IC50/nM | 3 | 10 | 1320 | 260 | 10 |
| MERS MPro IC50/nM | 187 | 245 | 32000 | 130 | 2360 |
| MERS/SARS2 enzyme IC50 ratio | 62 | 25 | 24 | 0.5 | 236 |
| other data | | low solubility | | poor Cathepsin L selectivity | |
| MERS CPE assay Vero E6 EC50 / uM | 4.4 | 17.5 | | MERS cellular data not reported | 5.3 |
| Comment | covalent | literature MERS cell data: CPE Huh7EC50: : 200nM | Wuxi MERS enzyme data - repeat @ Weizmann | covalent, literature data only | SARS2 Mpro analogue structure not covalent |

Carlsson et al: J. Am. Chem. Soc. 2022, 144 (7), 2905
Groutas et al: : J. Med. Chem. 2022, 65, 7818−7832

Enzyme: cell dropoff may be dependent on covalent/non covalent mode, or series permeability - much more data needed.

# Call for feedback



- We’re interested in how other people define their TPPs and TCPs

- Particularly interested where other groups are working on MERS +/- other huCoV

    - how are you considering efficacy
    - what are your safety criteria?
    - how are you translating those into your test cascades

# Questions from the Discussion



1. Have you considered time to steady state as a metric?
    a. we're more concerned with time to free Cmin/ED90 -fast to steady state is usually associated with highly cleared compounds, that would give a high peak-trough swing which might be more of a risk for in vivo toxicity
2. Why use bioavailability as the metric rather than dose?
    a. we should use both - but we'd tolerate a dose as high as is practically useful (3g/day?) whereas low bioavailability could lead to variability and thence variability in outcomes
3. What about having lung exposure compared to lung in the cascade?
    a. currently we'd thought of having it as a problem solving experiment of we have unexpected lack of efficacy in animal models as it's an expensive experiment to do, but we could do it in parallel with animal efficacy
4. Big debate question: is in vivo efficacy essential for pandemic preparedness - compared to efficacy in multiple cell models of a wide range of viruses and good predicted human pharmacokinetics
    a. the argument against mouse efficacy is that mice metabolise compounds easily, against that is the NIH and clinician interest in seeing in vivo efficacy in an animal model for progression as a risk reduction for taking into Phase 1. This remains a live argument.