Project title: A high-quality drug repurposing set

Principal Investigators: Anna-Lena Gustavsson (Karolinska Insitiutet)
Program research area: Drug discovery and repurposing of drugs/ COVID-19
Collaborators: available for all research groups throughout Sweden

- Aim: high-quality drug repurposing set from SPECS who has mirrored the set from Drug Repurposing Hub (Broad Institute), https://clue.io/repurposing
- Repurposing of drugs is a pragmatic strategy for rapidly advancing drug development. The benefits includes reduced cost, time and risks.
- Screening this set may provide information of the disease biology and play an important role as a profile benchmarking set towards newly identified compounds.
- Broads database on these compounds rich source for information!
- => 90 µL 10 mM DMSO stock solutions of 5280 cmpds (15 *384*-well plates)
- Screening volumes are available (nL assay ready plates), COVID-19 projects: 3000 sek – handling & shippments

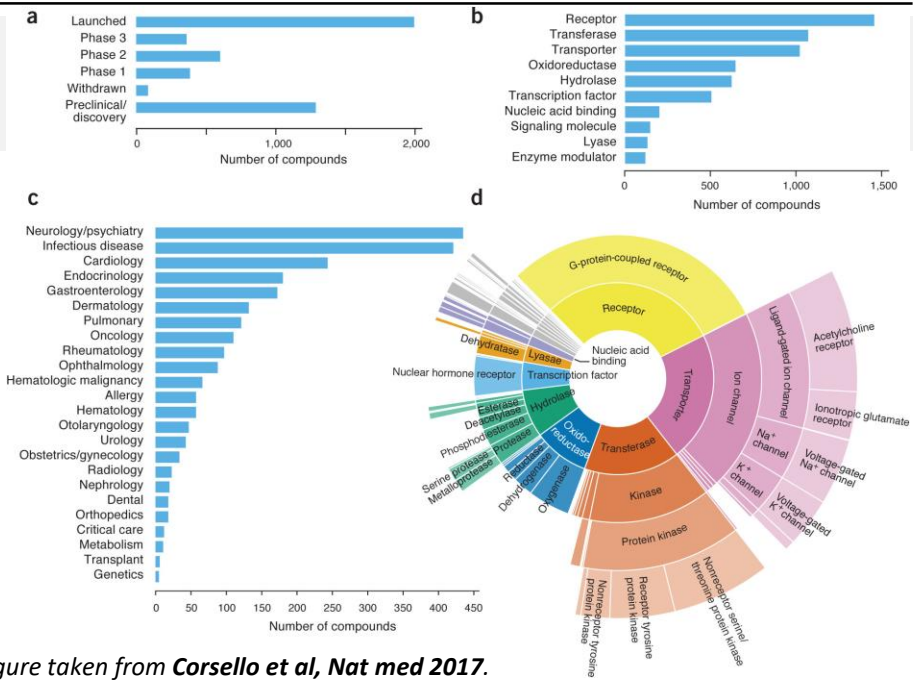


*Figure taken from **Corsello et al, Nat med 2017**.*
Drugs were identified, purchased, confirmed, and fully annotated.
*(**a**) Highest clinical phase achieved by each compound.*
*(**b**) Number of compounds per target category.*
Compounds with multiple targets might be indicated in more than one category.
*(**c**) Number of approved drugs for indications within each listed disease area.*
*(**d**) Classification of proteins targeted by library drugs.*
As expected, the library is enriched in drugs targeting kinases, GPCRs, and ion channels.

Spatial single cell mapping of SARS-CoV-2 interacting host proteins for quick and targeted drug repurposing

SciLifeLab

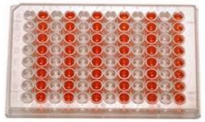
Principal Investigators: Charlotte Stadler. Dept. of Protein Science KTH and Päivi Östling, Oncology/Pathology KI)
Program research area: Drug discovery and repurposing of drugs/ COVID-19
Collaborators: Emma Lundberg (KTH), Anna-Lena Gustavsson (Chemical Biology Consortium Sweden-CBCS) and Ali Mirazami, Folkhälsomyndigheten (FHM)

May 2020

AIM: Identify translocating host cell proteins upon virus infection and drugs inhibiting these translocations

PROJECT PLAN:

Part 1: Stain 350 identified host cell SARS-CoV-2 interacting proteins in infected vs non infected cells



Infected vs non infected cells

+

THE HUMAN PROTEIN ATLAS

Target virus interacting proteins n ≈ 350

+

4 plex confocal microscopy

=

Subcellular protein localization - Computational Image Analysis

ImJoy
Deep learning made easy!

→ Translocating proteins = hits to part 2

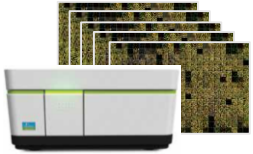
Part 2: Repurposing cell screen of ~ 5500 drugs for targeted readout of hits in part 1

~5500 approved drugs (15 x 384-well plates)

+

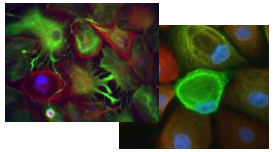
Target virus interacting proteins (n ~10-30)

+



4-plex confocal high-throughput microscopy (~60 -170 000 images)

=



Inhibit virus infected phenotype -- Computational Image Analysis

ImJoy
Deep learning made easy!

→ Approved drugs that inhibit a protein target for quick translation into treatment

FragCor – Fragment based NMR screen targeting SARS-Cov-2 proteins

SciLifeLab

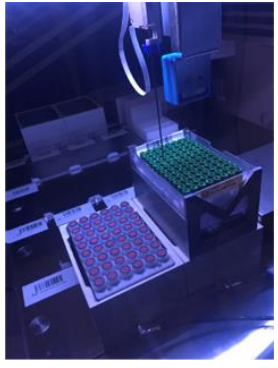
Principal Investigators: Göran Karlsson (University of Gothenburg)
Program research area: Drug discovery and repurposing of drugs/ COVID-19
Collaborators: Ulrika Brath, Gerhard Gröbner, Mattias Hedenström, Uwe Sauer, Erik Chorell, Anna Överby Wernstedt, Kristina Nyström

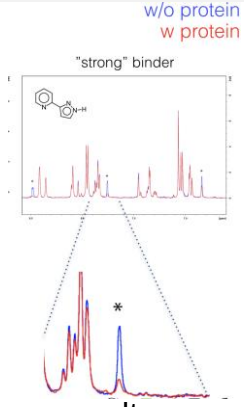
May 2020

- The main objective is to find suitable drug candidates against the SARS-CoV-2 virus. We focus on two essential viral mechanisms, viral binding and viral processing. Our aim is to identify suitable molecules from a large collection of already existing drugs and molecular fragment libraries that inhibit these mechanisms. The drugs or fragments can then be developed into a drug used to treat an ongoing Covid-19 infection.

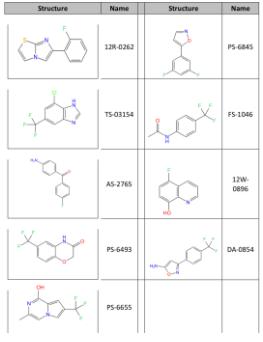
- The project includes three major steps,
  1) protein production
  2) screen molecules for ligand binding
  3) test molecular effect in cell assay

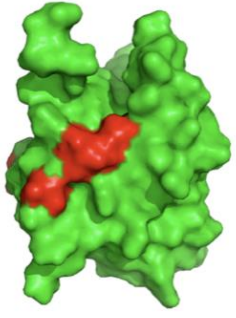
- Results so far
  - produced the major protease
  - screened > 1500 fragments for binding
  - identified 11 hits

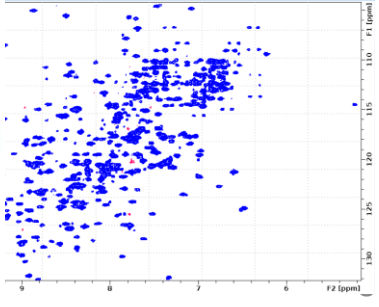




Prepare protein & ligands, run NMR, analyze results, reverse screen







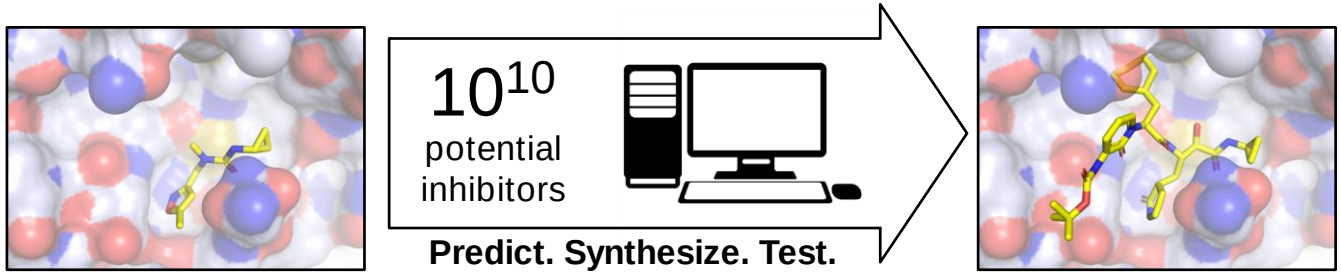
Discovery of SARS-CoV-2 Inhibitors by Virtual Screening of Ultra-large Chemical Space

SciLifeLab

Principal Investigators: Jens Carlsson (Uppsala University) and Helena Danielsson (Uppsala University)
Program research area: Drug discovery and repurposing of drugs/ COVID-19
Collaborators: Nevermore Covid project, Drug Discovery and Development (DDD) platform

May 2020

- The protein SARS-CoV 3CLpro (Main protease, M^{pro}) is essential for viral replication and a promising COVID-19 drug target.
- Atomic resolution structures of M^{pro} were recently determined and revealed small molecules (fragments) that are excellent starting points for drug development.
- We will use *in silico* methods to optimize the fragments into potent drug-like inhibitors of M^{pro}. Libraries with billions of compounds will be screened computationally, followed by synthesis and experimental testing of promising candidates.



Nevermore Covid
Establishing a drug discovery platform for coronavirus disease

May 2020

Principal Investigators: Kristian Sandberg, Uppsala University (Uppsala University, UU)

Program research area: Drug discovery and repurposing of drugs/ COVID-19

Collaborators: Helena Danielson (UU), Jens Carlsson (UU), Anja Sandström (UU), Johan Lennerstrand (UU), Åke Lundkvist (UU), Sonia Lain (Karolinska Institutet, KI), Iwan de Esch (Vrije University Amsterdam, VUA), Frank von Delft (University of Oxford, UO), Martin Walsh (UO), Fredrik Öberg (Medivir AB)

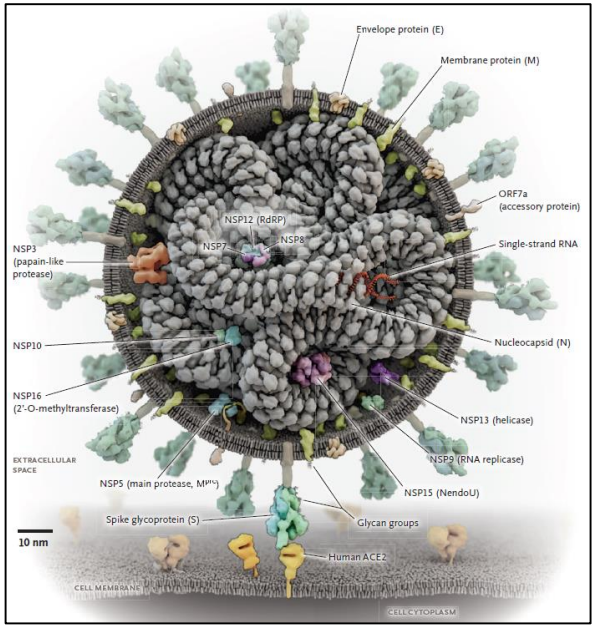
The SARS-CoV 3CLpro (Main protease, M^{pro} or Nsp5) is a chymotrypsin-like cysteine protease, essential for viral replication and a promising drug target for the treatment of coronavirus infections

Based on recent data on the structure of M^{pro}, three approaches will be conducted in parallell to identify small molecules that can be developed into drugs:

- Selections in DNA Encoded chemical libraries – library size: 10^6 - $4x10^9$, MW: 350-650
- Virtual screening – library size: 10^6 - 10^8, MW: 250 - 500
- Fragment based lead generation – library size: 10^2 - 10^3, MW: <250

A screening cascade is established to verify functionality of compounds in biochemical, biophysical and cellular assays and to allow for reiterative medicinal chemistry to improve inherent properties of small molecule ligands as drugs

An operative model for pre-competitive collaboration and on-line publication of key data will be developed for SciLifeLab DDD



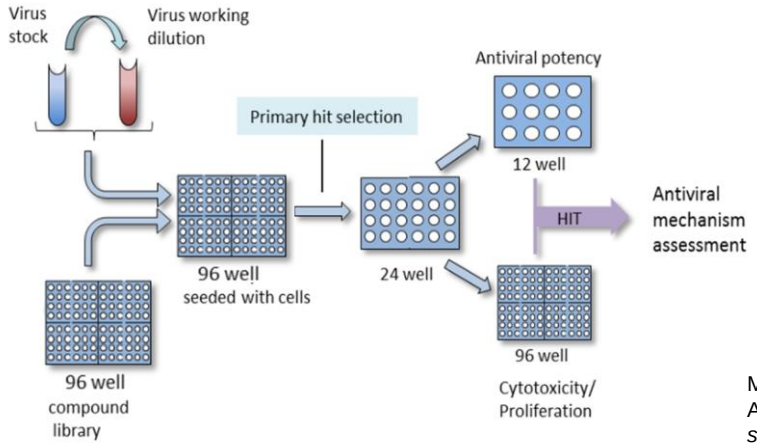
N. Eng. J. Med 2020 doi: 10.1056/NEJMcibr2007042

Rapid testing for treatment of Covid-19

Principal Investigators: Kristina Nyström (Gothenburg University)
Program research area: Drug discovery and repurposing of drugs/ COVID-19
Collaborators: Tomas Bergström, Edward Trybala, Magnus Gisslen and Martin Haraldsson

May 2020

- This project aims at testing the potential effect of available libraries of antiviral drugs and other approved drugs, originally targeting other virus infections and diseases, against SARS-CoV-2 in vitro.
- Prestwick drug repurposing library has been screened, data analysis underway for primary hit selection



Method for screening antivirals against SARS-CoV-2
Adapted from: (Lundin, A. (2013) *Candidate antivirals for treatment of respiratory syncytial virus and coronavirus infections: Identification and elucidation of mode of antiviral activity.* Doctoral, University of Gothenburg)

Distributed computing to generate the druggable conformational ensemble of sars-cov-2 proteins

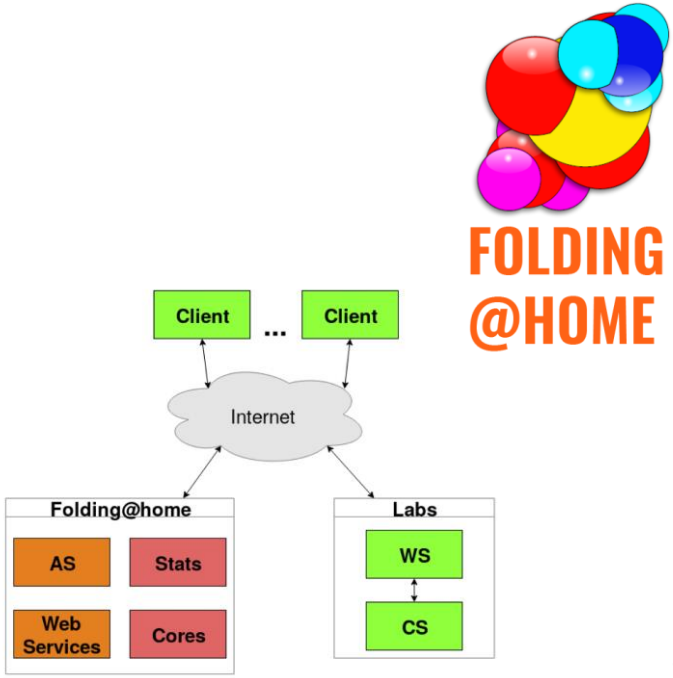
Principal Investigators: Lucie Delemotte (KTH), Erik Lindahl (SU/KTH), Berk Hess (KTH)
Program research area: Drug discovery and repurposing of drugs/ COVID-19
Collaborators: Greg Bowman (Washington U), John Chodera (MSKCC USA), Vincent Voelz (Temple U USA), Xuhui Huang (Hong Kong UST)

May 2020

- **Aim of project:** set up the infrastructure to use folding@home to generate the conformational dynamics of sars-cov-2 and human target proteins.

- **Methods:** F@h is a citizen-science, distributed computing platform to distribute expensive molecular dynamics simulations to computer time donors spread all-over the world.
    - https://foldingathome.org/

- **Impact on society:**
    - Generate druggable ensemble to go beyond a static structure for ensemble based drug repurposing and discovery (find cryptic pockets, characterize alternate states, effect of mutations etc…)
    - Outreach! We are directly talking to millions of donors, explaining the science of drug discovery, and empowering citizens to participate in scientific discovery and technology development. Interest from mainstream media has been enormous.



Multi-level profiling of Coronavirus-infected cells by combining Viral Entry Assays, Cell Painting, and DrugSEQ

SciLifeLab

Principal Investigators: Ola Spjuth (UppsalaUniversity)
Program research area: Drug discovery and repurposing of drugs/ COVID-19
Collaborators: Jordi Carreras-Puigvert (UU and KI), Marjo Puumalainen and Ulrika Warpman Berglund (KI), Sven Nelander (UU), Anna-Lena Gustavsson (CBCS)

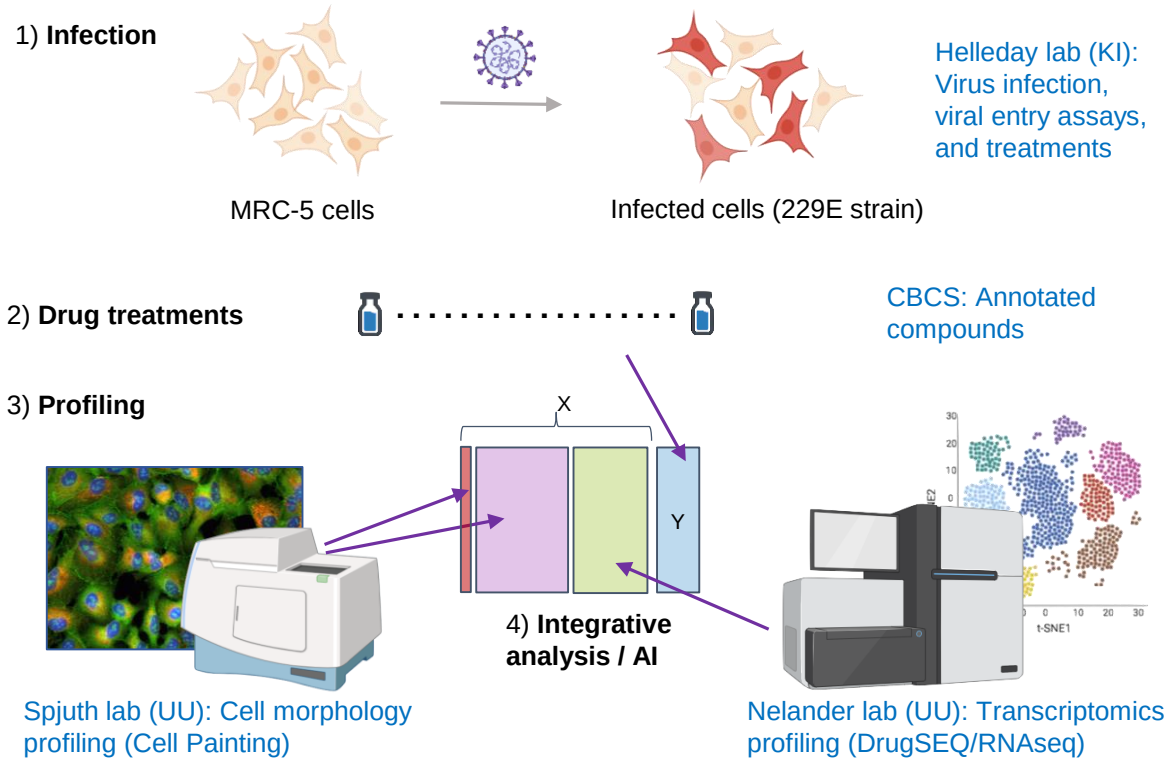
May 2020

Key aim: Profile coronavirus-infected cells using multiple profiling technologies

Phase 1: Proof-of-Principle [ongoing]
Establish relevant time points, virus dose, concentrations, logistics

Phase 2: Large-scale profiling
Compounds: Selected from SPECS repurposing library + spiked with other interesting compounds

Impact:
- High-quality integrative cell profiling dataset
- Insights into mechanistical understanding, effect of drugs, novel drug targets?
- Method, data and AI-models useful for profiling of new compounds



An adaptable therapeutic technology platform to treat SARS-CoV infections in immune suppressed individuals

Principal Investigators: ´ Sara Mangsbo (Uppsala University)
Program research area: Drug discovery and repurposing of drugs/ COVID-19
Collaborators: Helena Persson, SciLifeLab DDD platform, Johan Rockberg, KTH, Pierre Dönnes, SciCross AB

May 2020

Overall vision: clinical evaluation of an adaptable antibody-based platform for rapid vaccine implementation in a pandemic outbreak

Overall project goal: Identify COVID-19 derived epitopes for synthetic peptide vaccine development

Aim 1: peptide selection, synthesis and in vitro/in vivo assessment of immunogenicity

Aim 2: Finalize protein design for peptide delivery

Aim 3: Scale-up production preparation

Earlier and ongoing activities:

Litterature based search on SARS-CoV-2 epitopes

Protein delivery molecule functionality assessed (earlier project)

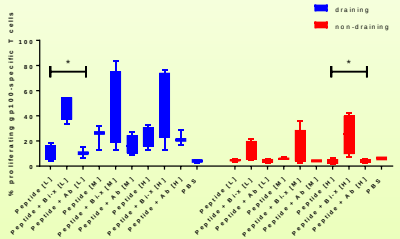
Serum/blood from COVID-19 recovered individuals collected and biobanked (ethical permit in place for drug evaluation in a blood based ex vivo system)

Methods:

Protein design, CD analyses, T cell activation studies, antibody binding evaluation, in vitro/in vivo work

Design: adaptable bispecific antibody (an alternative to antibody drug conjugates (ADCs))

In vivo T cell expansion



Earlier results:

- Antibody adjuvantability evaluation
- Production research grade protein material
- Peptide stability data (MS) with naked vs protein bound peptide
- Intracellular peptide release evaluation

Chemographic characterization of compounds binding to seven identified molecular targets from SARS-CoV-2

Anders Backlund – Reserachgroup Pharmacognosy, Dept. of Medicinal Chemistry

A global, 8D, map of NP chemical property space

1. **size, shape, polarisability....**
2. **aromaticity & conjugation related properties...**
3. **lipophilicity, polarity & H-bond donor capacity...**
4. **flexibility & rigidity...**
5. **electronegativity, number of N, halogens & amides...**
6. **number of rings, rotational bonds, amids & OH...**
7. **number of doubelbonds, oxygene & nitrogens....**
8. **aromatic & aliphatic OH, saturation, LAI...**

CTD1^{up} - binding to both ACE2 and RBD
NSP16 - methyltransferase
PLpro - papain-like proteinase
3CLpro - chymotrypsine-like cysteine protease'
RdRp - RNA-dependent RNA-polymerase
X-domain - of non-structural poly protein 1a.

Method is generally applicable...
Any compound or set can be used as 'hooks' to fish out similar compounds...