NIHR | Innovation Observatory

Protocol: Repurposing of therapeutics for SARS-CoV-2 an overview of current evidence.

October 2020

Authors: L Tanner, E Johnson, M Astin, F Beyer, D Ogunbayo, F Pearson, A Worsley, D Craig.

Director: Professor Dawn Craig
www.io.nihr.ac.uk info@io.nihr.ac.uk

Project Details

Contact Author:

Dr Fiona Pearson

Email: Fiona.Pearson@io.nihr.ac.uk

Project organisational affiliation:

NIHR Innovation Observatory, The Catalyst, Room 3.12, 3 Science Square, Newcastle Helix, Newcastle upon Tyne, NE4 5TG.

Team members and their organisational affiliations:

Louise Tanner[1, 2]; Eugenie Johnson[2]; Margaret Astin[2]; Fiona Beyer[1, 2]; Dapo Ogunbayo[1]; Fiona Pearson[1, 2]; Alan Worsley[3]; Dawn Craig[1, 2]

1. NIHR Innovation Observatory, The Catalyst, Room 3.12, 3 Science Square, Newcastle Helix, Newcastle upon Tyne. NE4 5TG.
2. Evidence Synthesis Group, Population Health Sciences Institute, Faculty of Medical Sciences, Newcastle University, Baddiley Clark Building, Newcastle Upon Tyne. NE2 4HH.
3. School of Pharmacy, Faculty of Medical Sciences, Newcastle University, King George VI Building, Newcastle upon Tyne. NE1 7RU.

Conflicts of interest:

LT, EJ, MA, FB, DP, FP, AW, DC: None

Anticipated start/finish date: 2/9/20 - 06/11/20

Review Tasks:

Preliminary searches	Completed
Piloting of study selection	Completed
Formal screening of search results against eligibility criteria	Completed
Data extraction	Completed
Risk of bias (quality) assessment	Piloted
Data Synthesis	Not started

Background

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) threatens public health at a global level, with over 29,000,000 cases in affected countries at present.(ECDPC 2020) Spain, France and the UK currently have the highest infection rates in Europe with 593,730, 387,252 and 371,125 cases respectively.(ECDPC 2020) Given the high infectivity of this virus and the fact that one in five infected become hospitalised with serious health consequences, it is vitally important to address how to improve treatment practices.(Zhonghua 2020) There are currently few approved medications for treating SARS-CoV-2. However, there are a range of drug therapies and a number of vaccines being evaluated to test their efficacy and safety.(NIHR-IO 2020) The treatments currently being evaluated range from those that target the cellular proteins essential to the life cycle of SARS-CoV-2, to those which reduce inflammation or act as anti-coagulants.(NIHR-IO 2020, Kindrachuk 2015, Pfefferle 2011, Lundin 2014, Hoffmann 2020, Cheng 2019)

Due to the urgent need for effective and accessible treatment for SARS-CoV-2, there have been specific efforts to repurpose or reposition approved and established drugs. This approach to identifying medications leads to a shorter drug development cycle than experimental drug development and requires upscaling of established production processes rather than generation of de novo systems.(Pushpakom 2019) The burden of the regulatory pathway and market access process is decreased and as generics for repurposed or repositioned drugs are often instantly available, the cost of drugs developed in this way tends to be lower.(Pushpakom 2019)

There is a burgeoning and disparate literature on repurposed or repositioned drug candidates for treatment of SARS-CoV-2 (from removal of the virus to recovery and rehabilitation). This review will provide an overview of evidence from hypothesis driving and preclinical studies which identify possible SARS-CoV-2 treatment candidates for clinical trial testing.

Aims and Objectives

Our aim is to give an up to date evidence overview of the drug repurposing research landscape and provide a list of possible treatment candidates for trial in relation to SARS-CoV-2 treatment (from removal of the virus to recovery and rehabilitation).

To achieve our aim our objectives are as follows:

- To identify any hypothesis driving studies for SARS-CoV-2 (e.g. use of computational drug discovery for redevelopment) that summarise potential repurposed drug candidates
- To identify any drug library screening studies (including high throughput screening studies or virtual, in-silico drug screens) that summarise potential repurposed drug candidates
- To identify any preclinical studies (including in vitro trials and studies on animal models) that summarise potential repurposed drug candidates for clinical trials
- To produce a map of potential repurposed drug candidates for clinical trial, critically appraising the evidence indicating each one as a potential candidate

Search strategy

Database: SARS-CoV-2-specific **COAP Living Evidence on COVID-19** https://ispmbern.github.io/covid-19/living-review/index.html

#1 (investigational) or (repurpose) or (repurposing) or (re-purpose) or (re-purposing) or (reposition) or (repositioning) or (re-position) or (re-positioning) or (reprofile) or (reprofiling) or (re-profile) or (re-profiling) or (off licence) or (off-licence) or (off license) or (off-license) or (unlicenced) or (unlicensed) or (off label) or (off-label)

Database(s): **Embase** 1996 to 2020 Week 38

#	Searches
1	sars coronavirus/ or sars-related coronavirus/
2	severe acute respiratory syndrome/
3	(coronavir* or corona virus* or HCoV* or ncov* or 2019nCoV or 2019 novel coronavirus or 2019 novel cov or cov 2 or cov2 or covid or covid19 or covid 19 or sars cov* or sarscov* or Sars coronavirus* or Severe Acute Respiratory Syndrome Coronavirus*).mp.
4	or/1-3
5	Middle East respiratory syndrome/
6	(middle east respiratory syndrome or mers or mers cov or mers coronavirus).mp.
7	or/5-6
8	(repurpos* or re purpos* or reposition* or re position* or reprofil* or re-profil* or off licenc* or off licens* or unlicen* or off label).mp.
9	(201911* or 201912* or 2020* or 2021*).dc.
10	4 and 8 and 9
11	7 and 8 and 9
12	10 or 11
13	limit 8 to covid-19
14	12 or 13

Database(s): **Scopus** 1996 to 2020 Week 38

((TITLE-ABS-KEY (coronavirus OR "corona virus" OR hcov* OR ncov* OR 2019ncov OR "2019-ncov" OR "2019 novel coronavirus" OR "2019 novel cov" OR "2019 novel-cov" OR "cov 2" OR "cov-2" OR cov2 OR covid OR covid19 OR "covid 19" OR "covid-19")) OR (TITLE-ABS-KEY ("sars cov*" OR "sars-cov*" OR sarscov* OR "Sars coronavirus" OR "Severe Acute Respiratory Syndrome Coronavirus")) OR (TITLE-ABS-KEY ("middle east respiratory syndrome" OR mers OR "mers cov" OR "mers-cov" OR "mers coronavirus" OR "mers-coronavirus")))

AND

(TITLE-ABS-KEY (repurpos* OR "re purpos*" OR "re-purpos*" OR reposition* OR "re position*" OR "re-position*" OR reprofil* OR "re profil*" OR "re-profil*" OR "off licenc*" OR "off-licenc*" OR "off licens*" OR "off-licens*" OR unlicen* OR "off label" OR "off-label"))

AND

(LIMIT-TO (PUBYEAR , 2021) OR LIMIT-TO (PUBYEAR , 2020) OR LIMIT-TO (PUBYEAR , 2019))

Inclusion and Exclusion Criteria

We will include primary studies of the following designs: in-vitro and in-vivo preclinical trials (such as studies on cell cultures, on animal models or non-human primates). We will also include drug library screens involving repurposed therapeutic agents targeting SARS-CoV-2 (including high throughput screening studies or virtual, in silico drug screens).

We will include studies describing potential adverse effects of the identified drugs, in addition to those describing potential therapeutic effects.

We will code but not include studies where the title or abstract does not specifically mention a drug only a drug category or repurposing/repositioning for SARS-CoV-2.

We will code but not include any pre-clinical studies where the drug(s) of interest is (are) now being evaluated in humans (i.e. within randomised controlled trials, controlled clinical trials, cohort studies, case studies, cross-sectional studies and case-control) or which have been evaluated and are now in human use. Should any identified drugs in trial or use not already be listed in NIHR-IO scans they will be flagged to the trial scanning team.

Reviews, letters, editorials and commentaries will be included if they fulfil the inclusion criteria.

We will code for but not include non-English language studies.

We will code for and include as plausible (given our timeline) any information we need to retrieve via inter-library loans or author contact.

Participants/population

There will be no restrictions by type of participants or population in studies reviewed.

Intervention(s), exposure(s)

We will include off-label drugs, vitamins and dietary supplements that have been approved by established regulatory authorities (e.g. the US Food and Drug Administration (FDA), European Medicines Agency (EMA)) for indications other than SARS-CoV-2 that could potentially be used in treating the SARS-CoV-2 infection and resultant physical morbidities.

Individual and combination therapies will be included.

The following will be excluded from the review:

- Biological targets for treatment (e.g. a disease pathway that could be influenced), with no drug indicated
- Prophylactic (preventative) interventions (e.g. SARS-CoV-2 vaccines and face masks - we are interested in treatments only)
- Complementary or alternative medicines
- Diagnostic tools (e.g. chest x-rays)
- Non-drug treatments (e.g. equipment, such as ventilator methods; patient management techniques)
- Any treatments already being used for treating SARS-CoV-2 patients in clinical trials or practice (e.g. convalescent plasma therapy)
- Drug(s) for treating the mental health impacts of SARS-CoV-2.

Comparator

Where relevant, there will be no restrictions on the type of comparator. Placebo, supportive care, other therapeutic interventions or no comparator will be accepted.

Main outcome(s)

The record should identify at least one drug candidate as a potential treatment for SARS-CoV-2 infection or resultant physical morbidities.

Mechanism of action

Where available we will extract data on the mechanism of action or the anatomical therapeutic chemical classification for each identified drug.

We will consult experts in pharmacy and drug development to validate the plausibility of each identified drug for treating SARS-CoV-2 and SARS-CoV-2-induced physical morbidities.

Data extraction (selection and coding)

Titles and abstracts will be screened independently by two reviewers (LT and EJ) in relation to the inclusion and exclusion criteria, with advice from a third reviewer where required (AW). Discrepancies will be resolved through discussion between reviewers and adjudication by a third reviewer (FP). The full texts of potentially relevant records will be screened using the same method.

A data extraction form will be created, piloted on a sample of included studies and refined. Data will be extracted by one reviewer with a proportion of extracted data checked for accuracy and completeness by a second reviewer (out of EJ, LT, MA and FP). The opinion of a third reviewer (AW or DO) or will be sought to resolve discrepancies in relation to the extracted data. Items on the pilot data extraction form will include the following: study citation; study design; population of interest; candidate drug(s); cell line (in-vitro) or animal model (in-vivo) tested; mechanisms of action or anatomical therapeutic chemical classification; pharmacokinetic and pharmacodynamic properties; primary outcomes reported; descriptive list of known adverse events or toxicity; and conclusions (e.g. subset of drugs identified as being most promising amongst those listed).

Quality assessment

The internal quality for *in vitro* and *in vivo* studies will be evaluated using the risk of bias (RoB) rating tool developed by the Office of Health Assessment and Translation. (Myatt 2018) This will be done by a single reviewer with a proportion of decisions quality assessed by a second reviewer. Each study will receive one of five possible responses: “Definitely Low Risk of Bias”, “Probably Low Risk of Bias”, “Probably High Risk of Bias”, “Definitely High Risk of Bias” or “Not Reported”, with a statement of justification. (Myatt 2018) The internal quality of in silico studies will be assessed using a checklist developed to assess the methodological quality of computational modelling studies. (Silva 2020) This will be done by a single reviewer with a proportion of decisions quality assessed by a second reviewer. An overall score will be given to each study calculated as percentage taken from the sum of rated questions divided by the sum of applicable questions. (Silva 2020) A decision will then be made by consensus of three reviewers as to whether each of these studies should be rated as “Definitely Low Risk of Bias”, “Probably Low Risk of Bias”, “Probably High Risk of Bias”, “Definitely High Risk of Bias” or “Not Reported”, with a statement of justification given.

Strategy for data synthesis

We will present a narrative synthesis of results indicating the amount and quality of evidence available upon each candidate as judged using the Drug Repositioning Evidence Level classification schema.(Oprea 2015) No statistical analysis is planned. Rather, a map will be produced indicating the volume and quality of research indicating each drug as a trial candidate and, if plausible, highlighting the drugs’ mechanism of action or the anatomical therapeutic chemical classification and the point in the SARS-CoV-2 disease pathway at which the drug acts.

Dissemination plans

A manuscript describing the work undertaken will be submitted to an academic journal for publication. Concurrent to the submission of this publication a synopsis of findings will be disseminated through the NIHR-IO website and direct engagement with key stakeholders.

Following publication, the manuscript and ancillary report will be made accessible on the NIHR-IO website. A lay summary will be produced and disseminated through relevant patient groups. Both the manuscript and ancillary report will be disseminated through relevant academic and clinical fora.

Acknowledgements

Funding sources/sponsors: This study/project is funded by the National Institute for Health Research (NIHR) [NIHRIO/project reference HSRIC-2016-10009]. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

References

1. European Centre for Disease Prevention and Control. 2020. COVID-19 Situation Update For The EU/EEA And The UK, As Of 12 October 2020. [online] Available at: <https://www.ecdc.europa.eu/en/cases-2019-ncov-eueea> [Accessed 13 October 2020].
2. Zhonghua, L., Xing, B., Xue, Z., Epidemiology Working Group for NCIP Epidemic Response; Chinese Center for Disease Control and Prevention. 2020. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. 41, pp. 145–151.
3. NIHR-IO. COVID-19 Therapeutics | Innovation Observatory. [online] Available at: http://www.io.nihr.ac.uk/report/covid-19-therapeutics/ [Accessed 16 Oct. 2020].
4. Kindrachuk, J., Ork, B., Hart, B., Mazur, S., Holbrook, M., Frieman, M., Traynor, D., Johnson, R., Dyall, J., Kuhn, J., Olinger, G., Hensley, L. and Jahrling, P., 2014. Antiviral Potential of ERK/MAPK and PI3K/AKT/mTOR Signaling Modulation for Middle East Respiratory Syndrome Coronavirus Infection as Identified by Temporal Kinome Analysis. Antimicrobial Agents and Chemotherapy, 59(2), pp.1088-1099.
5. Pfefferle, S., Schöpf, J., Kögl, M., Friedel, C., Müller, M., Carbajo-Lozoya, J., Stellberger, T., von Dall'Armi, E., Herzog, P., Kallies, S., Niemeyer, D., Ditt, V., Kuri, T., Züst, R., Pumpor, K., Hilgenfeld, R., Schwarz, F., Zimmer, R., Steffen, I., Weber, F., Thiel, V., Herrler, G., Thiel, H., Schwegmann-Weßels, C., Pöhlmann, S., Haas, J., Drosten, C. and von Brunn, A., 2011. The SARS-Coronavirus-Host Interactome: Identification of Cyclophilins as Target for Pan-Coronavirus Inhibitors. PLoS Pathogens, 7(10), p.e1002331.
6. Lundin, A., Dijkman, R., Bergström, T., Kann, N., Adamiak, B., Hannoun, C., Kindler, E., Jónsdóttir, H., Muth, D., Kint, J., Forlenza, M., Müller, M., Drosten, C., Thiel, V. and Trybala, E., 2014. Targeting Membrane-Bound Viral RNA Synthesis Reveals Potent Inhibition of Diverse Coronaviruses Including the Middle East Respiratory Syndrome Virus. PLoS Pathogens, 10(5), p.e1004166.
7. Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S., Schiergens, T., Herrler, G., Wu, N., Nitsche, A., Müller, M., Drosten, C. and Pöhlmann, S., 2020. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell, 181(2), pp.271-280.e8.
8. Cheng, Y., Williamson, P. and Zheng, W., 2019. Improving therapy of severe infections through drug repurposing of synergistic combinations. Current Opinion in Pharmacology, 48, pp.92-98.
9. Myatt, G.J., Ahlberg, E., Akahori, Y., Allen, D., Amberg, A., Anger, L.T., Aptula, A., Auerbach, S., Beilke, L., Bellion, P., Benigni, R., Bercu, J., Booth, E.D., Bower, D., Brigo, A., Burden, N., Cammerer, Z., Cronin, M.T.D., Cross, K.P., Custer, L., Dettwiler, M., Dobo, K., Ford, K.A., Fortin, M.C., Gad-McDonald, S.E., Gellatly, N., Gervais, V., Glover, K.P., Glowienke, S., Van Gompel, J., Gutsell, S., Hardy, B., Harvey, J.S., Hillegass, J., Honma, M., Hsieh, J.-H., Hsu, C.-W., Hughes, K., Johnson, C., Jolly, R., Jones, D., Kemper, R., Kenyon, M.O., Kim, M.T., Kruhlak, N.L., Kulkarni, S.A., Kümmerer, K., Leavitt, P., Majer, B., Masten, S., Miller, S., Moser, J., Mumtaz, M., Muster, W., Neilson, L., Oprea, T.I., Patlewicz, G., Paulino, A., Lo Piparo, E., Powley, M., Quigley, D.P., Reddy, M.V., Richarz, A.-N., Ruiz, P., Schilter, B., Serafimova, R., Simpson, W., Stavitskaya, L., Stidl, R., Suarez-Rodriguez, D., Szabo, D.T., Teasdale, A., Trejo-Martin, A., Valentin, J.-P., Vuorinen, A., Wall, B.A., Watts, P., White, A.T., Wichard, J., Witt, K.L., Woolley, A., Woolley, D., Zwickl, C. and Hasselgren, C. (2018). In silico toxicology protocols. Regulatory Toxicology and Pharmacology, 96, pp.1–17.
10. Silva, M., Freitas, B., Andrade, R., Espregueira-Mendes, J., Silva, F., Carvalho, Ó. and Flores, P. (2020). Computational Modelling of the Bioheat Transfer Process in Human Skin Subjected to Direct Heating and/or Cooling Sources: A Systematic Review. Annals of Biomedical Engineering, 48(6), pp.1616–1639
11. Pushpakom, S., Iorio, F., Eyers, P. et al. 2019. Drug repurposing: progress, challenges and recommendations. Nat Rev Drug Discov 18, pp.41–58
12. Oprea, T., Overington, J,P., 2015. Computational and Practical Aspects of Drug Repositioning. Drug Repositioning, Repurposing and Reuse, 1, pp.28-35

NIHR Innovation Observatory at Newcastle University
The Catalyst
Room 3.12, 3 Science Square
Newcastle Helix
Newcastle upon Tyne
NE4 5TG

Director: Professor Dawn Craig
W: www.io.nihr.ac.uk T: +44(0) 191 208 2259 E: info@io.nihr.ac.uk