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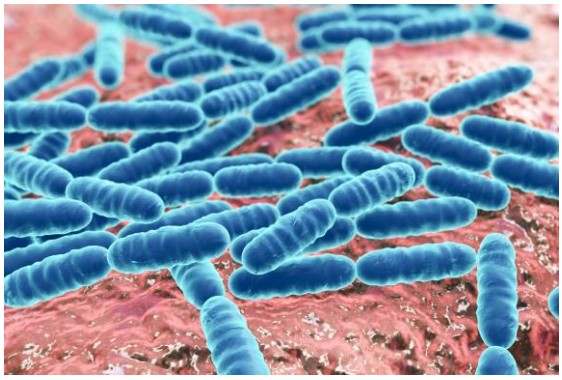
APC Microbiome Ireland: Culture to Product Platform



Key external stakeholders:

General public, health-care providers, pharmaceutical, biotechnology, veterinary and food sectors, gastrointestinal health research community and wider research community

Practical implications for stakeholders:

The Culture to Product Platform houses the APC Culture Collection (APC CC), a bank of bacterial cultures with potential for exploitation by researchers and industries across a range of sectors. Strains in the APC CC, with the exception of those already licensed, are available for use in industry projects subject to approval and agreement by the APC IP Manager and the Teagasc Technology Transfer Office (TTO). Work on this project has increased the potential for the commercialisation of strains in the APC CC.

Main results:

The APC Culture Collection (APC CC) currently houses over 2,700 bacterial strains of human, animal, food, clinical and environmental origin. The culture collection actively engages with the DPC Culture Collection in Teagasc, and the ELDERMET and INFANTMET Culture Collections (which together contain >15,000 bacterial isolates), enabling access to further strains of interest. The Culture to Product platform is responsible for the:

- curation and safe-guarding of APC Microbiome Ireland's bacterial cultures
- provision of data regarding the safety and quality of strains
- provision of traceability for IP protection and accountability

The culture collection includes strains with anti-*Clostridium difficile* properties, strains producing antimicrobials against a range of bacteria, and strains producing bioactive metabolites such as conjugated linoleic acid and exopolysaccharides. The APC CC was established in 2003 and is comprised of bacteria from screening initiatives by the Culture to Product platform and also from a range of APC projects. The Culture to Product platform also provides support in relation to strain isolation, characterisation and differentiation, microbiological techniques, animal trials and training across the APC and to industry projects.

Opportunity / Benefit:

The strains within this Culture Collection, with the exception of those already licensed to companies, are available to researchers within APC Microbiome Ireland and to industries and other research institutes with agreement from the APC IP manager and the Teagasc TTO.

Collaborating Institutions:

APC Microbiome Ireland, UCC

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Teagasc project team: Dr Mary Rea (PI), Dr Lisa Quigley, Dr Mairéad Coakley, Dr Siobhan Clarke, Dr Ewelina Stefanovic, Dr Veronica Peterson, Dr Matthew Aijuka, Dr Cecilia Soria & Prof Paul Cotter

External collaborators: Prof Paul Ross, Dr Harriet Schellekens, Dr Elena Pastor Cavada, Dr Valerie Ramirez, Dr Karen Dunn & Dr Brendan Curran, APC Microbiome Ireland and University College, Cork

1. Project background:

The APC Culture to Product platform is one of the platform technologies within APC Microbiome Ireland (http://apc.ucc.ie) that support this SFI Research Centre. The culture collection housed within the platform provides a safe and secure central repository for the bacterial strains underpinning the research of APC Microbiome Ireland. The platform is centre-wide, shared and supportive of research across all aspects of the APC and is also available for use by new and existing industry partners. The APC CC contains >2,700 strains (bio-safety level 1 and 2) from a range of origins (e.g. human, animal, food, clinical, environmental). Strains are sourced from APC and APC linked projects and include bifidobacteria, lactobacilli, lactococci, streptococci, clostridia, among others. Strains are catalogued and stored in duplicate at -80^{0}C. All available information on the strains is captured to provide background for continued research and future commercial exploitation. The systems linked to the acquiring and depositing strains provides traceability for IP protection and accountability.

2. Questions addressed by the project:

- Can we isolate novel bacterial strains of interest to human and animal health?
- How do selected strains perform when screened for probiotic and technological properties of interest?
- Can we expand our knowledge base on strains of interest e.g. antibiotic resistance profiling?
- We can determine the impact of strains and antimicrobials on the gut microbiota through co-culturing, colon models or animal models

3. The experimental studies:

Study 1: Culture collection curation, continued intake and supply of strains to and from the APC CC for Teagasc, UCC and to external Collections and updating of information on the strains in the database (to include data generated regarding the safety and quality of the strains).

Study 2: Isolation and characterisation of un-encumbered novel bacterial strains for the APC CC. These will include lactobacilli, bifidobacteria and strict anaerobes.

Study 3: Screening of lactobacilli for activity against *Clostridium difficile,* a common cause of health-care acquired diarrhoea which can result in a spectrum of disease from mild diarrhoea to life-threatening illness. Based on their ability to inhibit *C. difficile*, some strains will be studied in a murine model of *C. difficile* infection.

4. Main Result:

The APC Culture to Product Platform has provided support in relation to strain isolation, characterization and differentiation, microbiological techniques, animal trials and training across APC research themes and to industry projects.

- The project has increased the bank of unencumbered strains available (of human, environmental and animal origin) and increased knowledge of the potential probiotic and technological traits of selected strains. Hundreds of bacterial strains have also been lodged from a number of APC projects (e.g. human skin isolates, fish isolates and bacteria from human milk samples and faecal samples). Supporting information on these strains is catalogued and available in the APC CC database.
- A small subset of the strains have been screened for their probiotic potential and for their ability to produce antimicrobial compounds and bioactive molecules.
- A range of lactobacilli were screened as live bio-therapeutics for the treatment of *Clostridium difficile* infection.
- A *Lactobacillus gasseri* strain of human origin (*L. gasseri* APC 678) reduced *C. difficile* shedding and had a positive impact on the gut microbiome in a mouse model of *C. difficile* infection. The strain was patented and licensed to an industry partner. This work won the 2017 Bridge Network Invention of the Year; results contributed to a manuscript by Quigley *et al*., Frontiers Microbiol.
- Supernatants were generated from a range of lactobacilli and bifidobacteria and were screened in cell

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culture assays for modulation of G-protein coupled receptors (GPCRs) such as the ghrelin and serotonin receptors, which are linked to the regulation of appetite, food intake and satiety. Supernatants from selected bifidobacteria and lactobacilli of human origin demonstrated preliminarily activity. These strains are now being further screened and validated.

- The Culture to Product platform was involved in the antibiotic resistance profiling of 182 *Lactobacillus* type strains, discovering that >88% did not meeting EFSA guidelines; results contributed to a manuscript by Campedeli *et al*., AEM and resulted in an in-depth analysis of *L. gasseri* clindamycin resistance (manuscript in preparation).
- A range of strictly anaerobic bacteria were isolated from human faecal samples. These were identified (e.g. *Bacteroides*, *Ruminococcus* and *Alistipes* sp.) and are available for further research within the APC.
- The platform engaged in an animal trial (porcine model, n=40) to determine the impact of an antimicrobial compound, in an encapsulated and free form, on the porcine gut microbiota (results being analysed).
- Bacterial strain identification and differentiation and viability testing on probiotic products for industry partners.

5. Opportunity/Benefit:

The strains within this Culture Collection, with the exception of those already licensed to companies, are available to researchers within APC Microbiome Ireland and to industries and other research institutes with agreement from the APC IP manager and the Teagasc TTO.

6. Dissemination:

This project has resulted in a number of publications and has supported research published through other APC research themes. Personnel from the project have been represented at Teagasc and APC at Teagasc Open Days, Science Week events and APC Education and Public Engagement activities.

Main publications:

- Quigley, L.*, Coakley, M.*, Alemayehu, D., Rea, M.C., Casey, P.G., O'Sullivan, Ó., Murphy, E., Kiely, B., Cotter, P.D., Hill, C. and Ross, R.P. (2019) *Lactobacillus gasseri* APC 678 reduces shedding of the pathogen *Clostridium difficile* in a murine model. *Frontiers in Microbiology*. 10:273. doi: 10.3389/fmicb.2019.00273 (*equal contribution).
- Campedeli, I.*, Mathur, H.*, Salvetti, E., Clarke, S., Rea, M.C., Torriani, S., Ross, R.P., Hill, C. and O'Toole, P.W. (2018) Genus-wide assessment of antibiotic resistance in *Lactobacillus* spp. *Applied and Environmental Microbiology* 13;85(1). pii: e01738-18. doi: 10.1128/AEM.01738-18. (*equal contribution).
- Clarke, S.F., Soria, M.C., Rea, M.C., Coakley, M., Harris, H., Hill, C. and Ross, R.P. Strains of *Lactobacillus gasseri* exhibit "natural resistance" to clindamycin when compared to other lactobacilli within the *acidophilus* group (in preparation).

Other publications:

- Coakley, M., Rea, M., Quigley, L., Alemayehu, D., O'Sullivan, Ó., Cotter, P.D., Hill, C. and Ross, R.P. (2018) Lactobacilli as live biotherapeutics for the treatment of *Clostridium difficile* infection. Teagasc Research Impact Highlights 2017. p4.
- Coakley, M. (2018) Health promoting fatty acids and the gut microbiota. PhD. Teagasc, Moorepark, Fermoy; APC Microbiome Ireland, University College, Cork & School of Microbiology, University College, Cork.
- Ramirez, V.T., van Leuven, L., Coakley, M., Ross, R.P., Rea, M.C., Cryan, J. and Schellekens, H. (2017) Screening of bacterial-derived metabolites for Growth Hormone Secretagogue receptor 1a modulation. NeuroGASTRO 2017 hosted by the European Society of Neurogastroenterology and Motility (ESNM), Cork, Ireland. 24-26 August.
- Coakley, M., Rea, M., O'Sullivan, Ó., Stockdale, S., McCann, A., Hill, C. and Ross, R.P. (2016) Low levels of ampicillin and metronidazole have negligible effects on the human gut microbiota when assessed in an *ex-vivo* colon model. Poster and oral presentation at the Joint Microbiology Society and Irish Society of Immunology conference on "Exploring the microbe-immune system interface". Cork, Ireland. 1-2 September.

7. Compiled by: Mairéad Coakley and Paul Cotter

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