International Aspirin Foundation

Emerging Aspirin Investigator 2021

Award Ceremony

Hybrid event hosted at the
Caledonian Club, London and online
Friday 8th October 2021 2.00pm - 4.00pm.

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The International Aspirin Foundation's Emerging Aspirin Investigator Award recognises scientists in the early stages of their research career and encourages continued aspirin research. The number of applicants and the quality of science was excellent, and the Scientific Advisory Board (SAB) of the International Aspirin Foundation decided that as well as declaring a winner, a number of highly commended applicants' also warranted recognition. The work submitted showcased aspirin's wide range of applications including cardiovascular disease, cancer and obstetrics and the hybrid award ceremony allowed international participation and an interactive panel discussion with world leading experts.

Professor Ruth Langley introduced the winner and expressed the SAB's admiration for the multi-interdisciplinary nature of her work, the international collaborations, and the impact of her work for health and science.

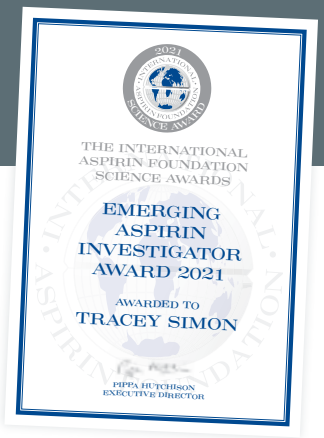
Emerging Aspirin Investigator

2021 Winner

Dr Tracey Simon

MD MPH, Hepatologist, Division of Gastroenterology,
Instructor of Medicine, Harvard Medical School. USA

Aspirin and Primary Prevention of Hepatocellular Carcinoma



Hepatocellular carcinoma (HCC) is the fifth most common cause of cancer worldwide and the second most lethal cancer with an increasing incidence and mortality worldwide. The World Health Organisation (WHO) currently project that there will be one million deaths from HCC in the year 2030. In the USA, HCC mortality rates are climbing faster than for any other cancer[1,2]. There has been a change in the risk factors for developing HCC from infection with hepatitis B and C viruses to new novel risk factors such as diet, lifestyle, obesity and type 2 diabetes.

Dr Simon discussed the current body of literature suggesting aspirin may prevent many gastrointestinal cancers, beyond colorectal cancer, including the hepatoprotective and chemoprotective effects of aspirin within the liver[3,4,5,6,7] as well as preclinical evidence for platelet activation and degranulation promoting non-alcoholic steatohepatitis (NASH) and HCC. Epidemiological evidence supporting a potential role for aspirin in HCC prevention has historically come from cohorts in Asia e.g., the Taiwan National Health Insurance database study which found a 29% lower HCC risk among aspirin users after accounting for potential confounders (HR 0.71,95% CI 0.58-0.86)[8].

In her work, Dr Simon sought to translate these epidemiological studies to a US population examining HCC risk and aspirin use in two prospective studies; the Nurse's Health Study and Health Professional follow up studies, involving 133,371 US adults.

Dr Simon found a dose dependent reduction in HCC risk in those using aspirin with adults who used greater than or equal to 1.5 aspirin tablets per week (approximately 70 mg of aspirin per day) benefitting from a 52% lower risk of incident HCC[9].

Next, Dr Simon sought to expand this work, using the Swedish database, to define the risk-benefit balance of aspirin for preventing HCC, in a population with established liver disease. Linking various disease registers Dr Simon found a 10-year absolute risk difference of – 4.3% (95% CI-5.0 to-3.6), with non-aspirin users experiencing a 10-year HCC cumulative incidence of 8.3% and aspirin users having a 4.0% incidence. The number needed to treat (NNT) to prevent one HCC was 23[10].

Overall, the study showed, after a further multivariate adjustment, that regular aspirin users had a 31% lower relative risk of HCC and a 27% lower-relative risk of liver-related mortality.

On further examination of those using aspirin (14,205) a duration of aspirin use and benefit ratio was established with those using aspirin for five years or more benefiting from a 43% lower HCC risk and a 37% lower risk of liver-related mortality. This also roughly corresponds to work with the Nurses' Health study and Health Professional follow up study in the US cohort.

The risk of bleeding was examined, and overall, no significant risk of major gastrointestinal bleeding was found. However, when this was further stratified into those with no cirrhosis, those with compensated cirrhosis and those with decompensated cirrhosis a trend was found showing likely increased risk of bleeding in those with decompensated disease[10].

Dr Simon's current research has a focus on addressing more gaps in aspirin and HCC chemoprevention research such as the safety of aspirin use in cirrhosis, HCC biomarkers modulated by aspirin and the potential role of low-dose aspirin (81 mg) to reverse NASH and fibrosis in established non-alcoholic fatty liver disease (NAFLD).

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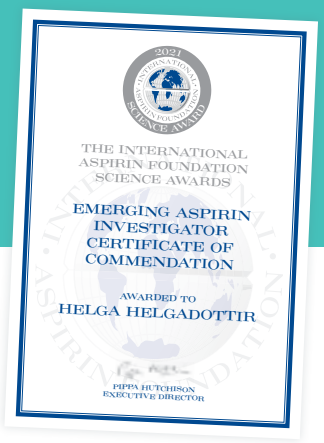
Emerging Aspirin Investigator

Highly Commended Candidate

Dr Helga Helgadóttir

Associate Professor, Faculty of Pharmaceutical Sciences, University of Iceland.

The prophylactic use of aspirin to prevent the development of pre-eclampsia in pregnancy.



Dr Helga Helgadóttir studied the prophylactic use of aspirin to prevent pre-eclampsia with a particular interest in understanding the mechanism behind aspirin's mode of action in this setting. Dr Helgadóttir studies are part of ASPRE, a double-blind, multi-centre trial across Europe. The trial compared aspirin, 150 mg daily, with placebo in women who were at risk for pre-eclampsia and showed that aspirin was able to prevent pre-eclampsia especially when this occurs early in pregnancy.

It was interesting to note that the study showed that aspirin can prevent 80% of pre-eclampsia at < 32 weeks; 63% of pre-eclampsia at <37 weeks but only 15% of pre-eclampsia > 37 weeks (ASPRE).

From her mechanistic studies, Dr Helgadóttir, concluded that aspirin causes direct vasodilation in isolated uterine and mesenteric arteries from non-gravid rats and the effect is endothelium-dependent in late-gravid rats. The mechanism of action for aspirin is different in the two vascular beds: the reproductive and the splanchnic circulation. Vessel sensitivity to aspirin changes with gestational age.

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Helgadóttir H, Tropea T, Gizurarson S, Mandalà M. Endothelium-Derived Hyperpolarizing Factor (EDHF) Mediates Acetylsalicylic Acid (Aspirin) Vasodilation of Pregnant Rat Mesenteric Arteries. *International Journal of Molecular Sciences* 2021; 22(18):10162 https://doi.org/10.3390/ijms221810162

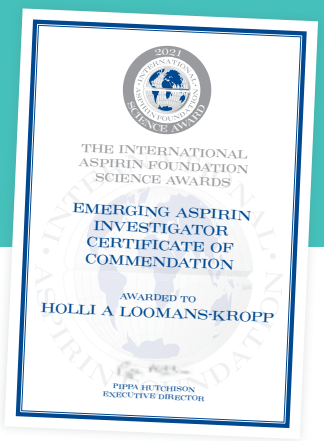
Emerging Aspirin Investigator

Highly Commended Candidate

Dr Holli Loomans-Kropp

Postdoctoral Fellow,
GIORG National Cancer Institute (NCI), USA.

The association between aspirin use and cancer risk in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial.



Dr Loomans-Kropp presented a summary of studies examining the association between aspirin use and cancer in the prostate, lung, colorectal and ovarian (PLCO) cancer screening trial. Dr Loomans Kropp utilized her interdisciplinary training in epidemiology and cancer biology to develop, initiate, and execute projects exploring prevention modalities for gastrointestinal malignancies, most notably colorectal cancer (CRC). Two studies were conducted, first one to examine the association of aspirin use with mortality risk (all-cause cancer, gastrointestinal [GI] cancer and CRC) among older adult participants in the PLCO and a second study to evaluate aspirin use with breast, bladder, oesophageal, gastric, pancreatic and uterine cancer incidence and survival among older adults in the PLCO.

Dr Loomans-Kropp found aspirin use was associated with reduced risk of all examined causes of death in the PLCO participants aged 65 and older but this effect is dependent upon the frequency of use, the length of use and the individuals BMI. She also discovered that in the PLCO, aspirin use three or more times per week was not associated with the incidence of bladder, breast, oesophageal, gastric, pancreatic or uterine cancer but was found to be associated with a reduced risk of bladder and breast cancer mortality.

Dr Loomans-Kropp is working with the ColoCare (a prospective cohort of individuals newly diagnosed with primary CRC) study group to study the biological mechanisms surrounding cancer incidence and aspirin use. Preliminary results, from this ongoing study, suggest prolonged changes in circulating inflammation associated proteins with aspirin use. Dr Loomans-Kropp plans to expand upon this research base to better understand the contextual mechanisms of aspirin and how these mechanisms can be exploited for generalized and precision prevention.

References

Loomans-Kropp H.A., Pinsky P, Cao Y et al. Association of aspirin use with mortality risk among older adult participants in prostate, lung, colorectal, and ovarian cancer screening trial. *JAMA Network Open.* 2019; 2(12):e1916729 doi:10.1001/jamanetworkopen.2019.16729

Loomans-Kropp HA, Pinsky P and Ulmar A. Evaluation of aspirin use with cancer incidence and survival among older adults in prostate, lung, colorectal, and ovarian cancer screening trial. *JAMA Network Open.* 2021; 4(1):e2032072. Doi:10.1001/jamanetworkopen.2020.32072

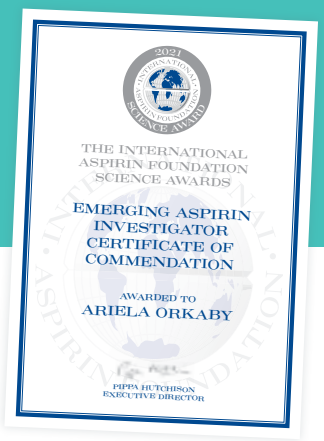
Emerging Aspirin Investigator

Highly Commended Candidate

Dr Ariela Orkaby

MD MPH Geriatrics and Preventative Cardiology, Assistant Professor of Medicine, Harvard Medical School, Brigham and Women's Hospital, VA Boston Healthcare System GRECC, USA.

Is aspirin use associated with a decreased risk of frailty and functional limitation in older men?



Dr Orkaby explained that one of the greatest fears among older adults is losing their functional independence and becoming frail. To help with this Dr Orkaby turned to aspirin which at low doses has antithrombotic properties and at high doses analgesic and antipyretic properties and at both high and low doses an anti-inflammatory effect. Frailty and cardiovascular disease are bidirectionally related and one of the key players in this is inflammation. Dr Orkaby therefore hypothesised that slow gait speed and frailty, which are both interrelated with cardiovascular disease, could potentially be mediated by aspirin

Since decrease in muscle mass is known as a hallmark of frailty, Dr Orkaby investigated some of the basic science and found that salicylates improve muscle regeneration in mice. Then, Dr Orkaby analysed data from the Physician's Health Study (PHS) and found that regular aspirin use, over 15 years of follow up, is associated with 15% lower odds of prevalent frailty, with no statistically significant interactions for age, history of CHD, arthritis, prior GI bleed and significant interaction for exercise (Orkaby 2020). She also found that regular aspirin use was associated with a faster walking speed. One strength of this study is the average age at the start of aspirin use was 58 years, an age at which bleeding risk is low and there is time to change the inflammatory milieu that leads to frailty. This contrasts with the Aspirin in Reducing Events in the Elderly (ASPREE) trial which enrolled adults 70 and older and found no benefit for their primary outcome of disability and dementia free survival, with an increased risk of bleeding. It is likely that preventive strategies for frailty must begin earlier in life.

References

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Orkaby A, Yang L, Dufour AB et al. Association between long-term aspirin use and frailty in men: The Physicians' Health Study. *J of Gerentol A Biol Sci* Med Sci 2021, Vol 76, no 6, 1077-1083 doi:10.1093/Gerona/glaa233

Orkaby AR, Dufour AB, Yang L Long-term aspirin use and self-reported walking speed in older men: The Physicians' Health Study. *J Frailty Aging* 2021 https://doi.org/10.14283/jfa.2021.36

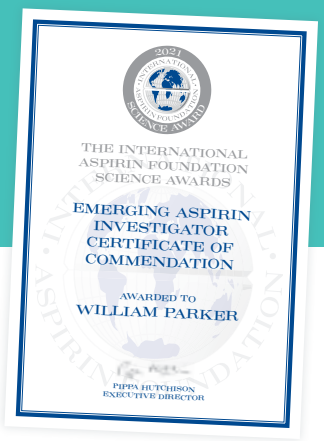
Emerging Aspirin Investigator

Highly Commended Candidate

Dr William Parker

MA MB BChir PhD SRPharmsS MRCS MRCP, British Heart Foundation Clinical Research Training Fellow in Cardiology, University of Sheffield and Registrar in Cardiology at Sheffield Teaching Hospitals NHS Foundation Trust, UK.

Optimising aspirin dosing for patients with high-risk coronary syndromes: the WILLOW programme.



The focus of Dr Parker's work is around optimising dosing of aspirin for patients receiving combination antithrombotic therapy for coronary artery disease (CAD). In patients without high background ischaemic risk or risk factors that increase the chance of bleeding, it is becoming apparent that early de-escalation to a single agent maybe a safe and effective strategy. However, in those with high ischemic risk and no risk factors for bleeding there is good evidence for continuing longer term dual antiplatelet therapy and this is reflected in the current ESC Chronic Coronary Syndromes recommendations[1,2]. This is because despite potent $PY2_{12}$ inhibition aspirin continues to exert an additional effect particularly upon collagen induced platelet aggregation responses and Dr Parker has demonstrated this in experiments in vitro[3]. An increase in reactivity when patients receiving DAPT discontinue aspirin and transition to ticagrelor monotherapy can also be seen in a sub study of the GLOBAL LEADERS study[4].

Various factors can affect the reliability of aspirin treatment and conditions that can increase platelet turnover such as obesity, diabetes, smoking and procedural intervention can increase peak trough variation and effect. Multiple daily dosing of aspirin has been shown to improve its consistency of effect in these groups[5]. Dr Parker hypothesised that using a lower than standard dose of aspirin given twice a day might offer a better profile of effect during combination antithrombotic therapy for cardiovascular disease when compared with current standard of care low-dose aspirin. Dr Parker found a candidate regimen of 20 mg of aspirin twice daily reduced the peak trough variation on both COX-1 inhibition and haemostasis but maintained adequate 24-hour consistency. After characterising the pharmacodynamic aspects of his work Dr Parker hopes to progress to feasibility studies for adopting this approach in wider clinical practice before seeking to conduct large clinical outcome trials.

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Ceremony concluding remarks

Professor Patrono concluded the meeting commenting on this very interesting and stimulating afternoon of excellent science and thanked and congratulated the candidates for their interesting scientific work and wished them the best for their future achievements. Professor Patrono also thanked the IAF for organising this event and GL Pharma for supporting it.

IAF Executive Director, Pippa Hutchison thanked everyone for attending this hybrid meeting; for their passion and dedication to aspirin and hoped they will all continue to explore this amazing medicine throughout their careers.

Further information

Individual presentations can be seen at
https://www.aspirin-foundation.com/awards/emerging-aspirin-investigator-award-2021/

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