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'Central Dogma of Molecular Biology': Should 'Dogmas' and 'Cult Figures' Have Any Place in Science?

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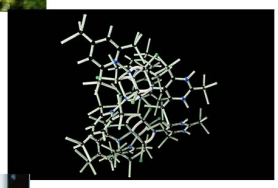

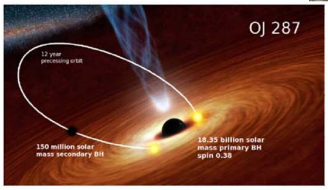

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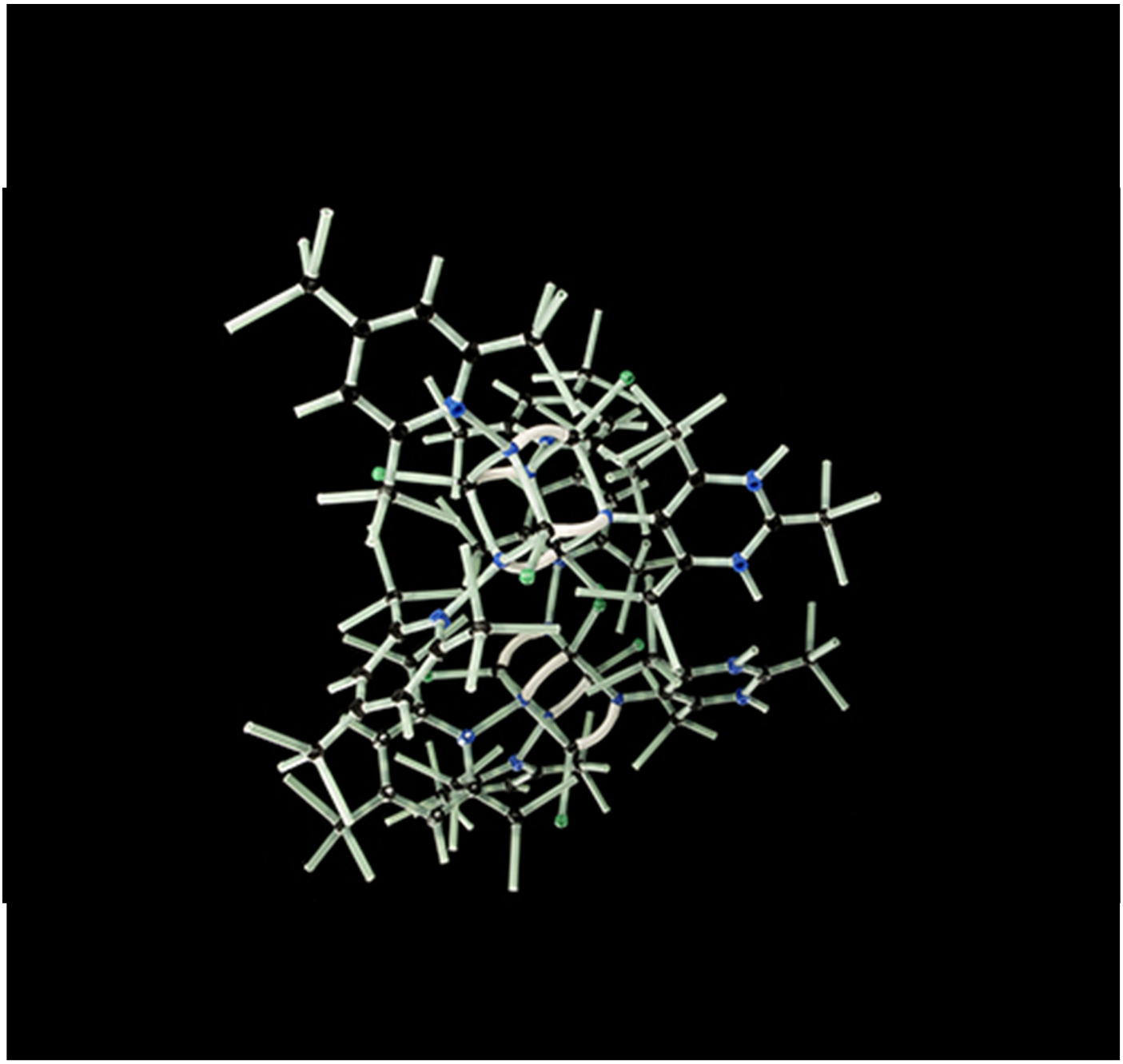
Vitamin D Insufficiency (VDI) Leads to Severe COVID-19 Symptoms

Easily correctable condition of Vitamin D Insufficiency (VDI) has very severe implications for COVID-19. In countries worst affected by COVID-19 such as Italy, Spain and Greece, Vitamin D insufficiency (VDI) rates were high in the range of 70-90%.; on the other hand, in Norway and Denmark, where COVID-19 was less severe, VDI rates were 15-30% suggesting strong correlation between VDI and COVID-19. It is hypothesized that VDI aggravates COVID-19 severity by its prothrombic effects and deregulation of immune response. Furthermore, in Wuhan, COVID-19 Associated Coagulopathy (CAC) was present in 71.4% of non-survivors vs. 0.6% in survivors. Patients with VDI having severe COVID-19 symptoms also had CAC, viz. blood clotting in micro vessels that was associated with high mortality.

The COVID-19 pandemic that has infected ~6.4 million people worldwide and resulted in death of ~380,000 people has brought the entire world on its knees with respect to the economic state of



above-mentioned gases plus smaller amounts of carbon monoxide and carbon dioxide. The relevance of Miller-Urey experiments was questioned by the scientific fraternity for a number of years, who thought that the gas mixture used in their research was too reducing with respect to the conditions that existed on primordial Earth. A number of theories pointed towards a neutral atmosphere containing an excess of CO_2 with N_2 and water vapor4. However, a neutral atmosphere has also been identified as a plausible environment for the synthesis of amino acids5. In addition, for proteins to act as origins of life, they need to self-replicating leading to a combination of different proteins to cater to different reactions taking place in an organism.

rest had even lower levels. Out of 11 patients in ICU, 62.5% had CAC (COVID-19 Associated Coagulopathy) while 92.5% had lymphopenia suggesting that VDI aggravates COVID-19 severity by its prothrombic effects and deregulation of immune response4. In Wuhan, CAC was present in 71.4% of non-survivors vs. 0.6% in survivors5. Vitamin D has been shown to play an essential role in modulating both the innate and adaptive immune response6, 7 while VDI is associated with increased risk of CVD and death8.

In another retrospective multicentre study of 212 cases with laboratory-confirmed infection of SARS-CoV-2, serum vitamin D levels were lowest in critical cases, but highest in mild cases9. Data analysis revealed that for each standard deviation increase in serum vitamin D, the odds of having a mild clinical outcome rather than a severe one was increased ~7.94 times, while interestingly, the odds of having a mild clinical outcome rather than a critical outcome were increased ~19.61 times9. This suggests that an increase in vitamin D levels in the body could either improve clinical outcomes, while a decrease in vitamin D levels in the body could intensify the clinical outcomes in COVID-19 patients.

These studies showing a positive/improved clinical response in COVID-19 patients with increased levels of vitamin D and a negative/poor clinical response with low vitamin D levels warrant further investigation on the role of vitamin D in COVID-19 disease and provides a way forward for clinicians and policy makers to undertake large population trials to evaluate this as a preventive measure to fight against COVID-19.

References:

1. Weiss SR and Navas-Martin S. 2005. Coronavirus pathogenesis and the emerging pathogen severe acute respiratory syndrome coronavirus. Microbiol. Mol. Biol. Rev. 2005 Dec;69(4):635-64. DOI: https://-doi.org/10.1128/MMBR.69.4.635-664.2005

2. Soni R., 2020. ISARIC Study Indicates How Social Distancing Could Be Fine-tuned in Near Future to Optimise 'Protecting Lives' and 'Kickstart National Economy'. Posted May 01, 2020. Scientific European. Available online at https://www.scientificeuropean.co.uk/isaric4c-study-indicates-how-social-distancing-could-be-fine-tuned-in-near-future-to-optimise-protecting-lives-and-kickstart-national-economy Accessed on 30 May 2020.

3. Scharla SH., 1998. Prevalence of subclinical vitamin D deficiency in different European countries. Osteoporosis Int. 8 Suppl 2, S7-12 (1998). DOI: https://doi.org/10.1007/PL00022726

4. Lau, FH., Majumder, R., et al 2020. Vitamin D insufficiency is prevalent in severe COVID-19. Pre-print medRxiv. Posted 28 April 2020. DOI: https://-doi.org/10.1101/2020.04.24.20075838 or https://www.medrxiv.org/content/10.1101/2020.04.24.20075838v1

5. Tang N, Li D, et al 2020. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. Journal of Thrombosis and Haemostasis 18, 844–847 (2020). First published:19 February 2020. DOI: https://-doi.org/10.1111/jth.14768

6. Liu PT., Stenger S., et al. 2006. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. Science 311, 1770–1773 (2006). DOI: https://doi.org/10.1126/science.1123933

7. Edfeldt K., Liu PT., et al 2010. T-cell cytokines differentially control human monocyte antimicrobial responses by regulating vitamin D metabolism. Proc. Natl. Acad. Sci. U.S.A. 107, 22593–22598 (2010). DOI: https://doi.org/10.1073/p-nas.1011624108

8. Forrest KYZ and Stuhldreher WL 2011. Prevalence and correlates of vitamin D deficiency in US adults. Nutrition Research 31, 48–54 (2011). DOI: https://-doi.org/10.1016/j.nutres.2010.12.001 ■

affairs. With the vaccine still far in sight, there is a need for a deeper understanding of the disease so that adequate precautions can be taken to avoid getting inflicted with the disease. The age old saying, "Prevention is better than cure", is extremely apt in case of COVID-19 disease as the entire scientific world is grappling to understand the nature and complexity of this disease so as to find preventive measures to control its spread.

A number of studies have been performed to understand the life cycle of the SARS-CoV-2 virus, its virulence in people of different ages and the recovery rate of the people infected with the virus1,2. One of the factors that could have been overlooked is the Vitamin D status of the populations that could influence the severity of COVID-19 disease as more people are advised to stay indoors. In studies across Europe, it has been observed that COVID-19 had been severe in Italy, Spain and Greece which had vitamin D insufficiency (VDI) rates of 70-90% as compared to VDI of 15-30% in Norway and Denmark where the COVID-19 disease was not as severe 3. People's diet in Scandinavian countries are rich in Vitamin D due to high fatty fish intake and dairy supplements that are fortified with Vitamin D3.

In a recent study performed at a single, tertiary care academic medical centre on 20 subjects, a direct correlation was found between the levels of Vitamin D and the severity of COVID-19 disease. 11 of these patients were admitted to ICU and had VDI, 7 of them having levels below 20ng/mL while

B) If the primordial soup provided conditions for building blocks of DNA and/or RNA to be formed, then either of these could have been the genetic material. The research until now favoured RNA to be the genetic material for the origin of life forms due to their capability of folding upon itself, existing as a single strand and acting as an enzyme6, capable of making more RNA molecules. A number of self-replicating RNA enzymes7 have been discovered over the years suggesting RNA to be the starting genetic material. This was further strengthened by the research performed by John Sutherland's group that led to the formation of two bases of RNA in an environment similar to primordial soup by including phosphate in the mixture8. Formation of RNA building blocks has also been shown by simulating a reducing atmosphere (containing ammonia, carbon monoxide and water), similar to one used in Miller-Urey's experiment and then passing electric discharges and high-power lasers through them9. If RNA is to be believed to be the originator, then when and how did DNA and proteins come into being? Did DNA develop as a genetic material later because of the unstable nature of RNA and proteins followed suit. Answers to all these questions still remain unanswered.

C) The third scenario that DNA and RNA can co-exist in the primordial soup that led to the origin of life came from studies published on 3rd June 2020 by John Sutherland's group from the MRC Laboratory at Cambridge, UK. The researchers simulated the conditions that existed on a primordial Earth billions of years ago, with shallow ponds in the lab. They first dissolved chemicals that form RNA in water, followed by drying and heating them and then subjecting them to UV radiation that simulated sun's rays existing in primordial time. This not only led to the synthesis of the two building blocks of RNA but also of DNA, suggesting that both nucleic acids co-existed at the time of origin of life10.

Based on the contemporary knowledge existing today and honouring the central dogma of molecular biology, it seems plausible that the DNA and RNA co-existed that led to origin of life and protein formation came/occurred later.

However, the author wishes to speculate another scenario where all the three important biological macromolecules, viz. DNA, RNA and protein existed together in the primordial soup. The messy conditions that existed in the primordial soup involving the chemical nature of earth's surface, volcanic eruptions and presence of gases such as ammonia, methane, carbon monoxide, carbon dioxide along with water may have been ideal for all macromolecules to be formed. A hint of this has been provided by research done by Ferus et al., where nucleobases were formed in the same reducing atmosphere9 used in Miller-Urey's experiment. If we are to believe in this hypothesis, then during the course of evolution, different organisms adopted one or the other genetic material, that favoured their existence moving forward.

However, as we try to understand the origin of life forms, much further research is required to answer the fundamental and pertinent questions about how life originated and propagated. This would require an "out-of-the-box" approach without relying on any prejudices introduced in our thinking by the current dogmas followed in science.

References:

1. Miller S., 1953. A Production of Amino Acids under Possible Primitive Earth Conditions. Science. 15 May 1953: Vol. 117, Issue 3046, pp. 528-529 DOI: https://doi.org/10.1126/science.117.3046.528

2. Bada JL, Lazcano A. et al 2003. Prebiotic Soup–Revisiting the Miller Experiment. Science 02 May 2003: Vol. 300, Issue 5620, pp. 745-746 DOI: https://-doi.org/10.1126/science.1085145

3. Miller SL and Urey HC, 1959. Organic Compound Synthesis on the Primitive Earth. Science 31 Jul 1959: Vol. 130, Issue 3370, pp. 245-251. DOI: https://-doi.org/10.1126/science.130.3370.245

4. Kasting JF, Howard MT. 2006. Atmospheric composition and climate on the early Earth. Philos Trans R Soc Lond B Biol Sci 361:1733–1741 (2006). Published:07 September 2006. DOI: https://-doi.org/10.1098/rstb.2006.1902

Molecular Origin of Life: What Formed First – Protein, DNA or RNA or a Combination Thereof?

'Several questions about origin of life have been answered, but much remains to be studied" said Stanley Miller and Harold Urey way back in 1959 after reporting laboratory synthesis of amino acids in primitive earth conditions. Many advances down the line yet the scientists have long been grappling with a fundamental question – which genetic material was first to be formed on the primitive earth, DNA or RNA, or a bit of both? There is evidence now to suggest that DNA and RNA both may have co-existed in the primordial soup from where the life forms may have evolved with respective genetic materials.

THE central dogma of molecular biology states that DNA makes RNA makes proteins. Proteins are responsible for majority, if not all the reactions taking place in an organism. The entire functionality of an organism is majorly dependent upon their presence and interaction of protein molecules. According to central dogma, proteins are produced by the information contained in DNA which is converted to functional protein via a messenger called RNA. However, it is possible that proteins themselves can survive independently without any DNA or RNA, as is the case with prions (misfolded protein molecules that do not contain DNA or RNA), but can survive on their own.

Thus, there can be three scenarios for the origin of life.

A) If the proteins or its building blocks were able to form abiotically during the atmosphere that existed billions of years ago in primordial soup, proteins can be termed as the basis of origin of life. The experimental evidence in its favour comes from the famous experiment by Stanley Miller1, 2, which showed that when a mixture of methane, ammonia, water and hydrogen are mixed together and circulated past an electric discharge, a mixture of amino acids is formed. This was again corroborated seven years later3 in 1959 by Stanley Miller and Harold Urey stating that the presence of

5. Cleaves HJ, Chalmers JH, et al 2008. A reassessment of prebiotic organic synthesis in neutral planetary atmospheres. Orig Life Evol Biosph 38:105–115 (2008). DOI: https://-doi.org/10.1007/s11084-007-9120-3

6. Zaug, AJ, Cech TR. 1986. The intervening sequence RNA of Tetrahymena is an enzyme. Science 31 Jan 1986: Vol. 231, Issue 4737, pp. 470-475 DOI: https://doi.org/10.1126/-science.3941911

7. Wochner A, Attwater J, et al 2011. Ribozyme-Catalyzed Transcription of an Active Ribozyme. Science 08 Apr: Vol. 332, Issue 6026, pp. 209-212 (2011). DOI: https://doi.org/10.1126/-science.1200752

8. Powner, M., Gerland, B. & Sutherland, J., 2009. Synthesis of activated pyrimidine ribonucleotides in prebiotically plausible conditions. Nature 459, 239–242 (2009). https://doi.org/10.1038/nature08013

9. Ferus M, Pietrucci F, et al 2017. Formation of nucleobases in a Miller–Urey reducing atmosphere. PNAS April 25, 2017 114 (17) 4306-4311; first published April 10, 2017. DOI: https://-doi.org/10.1073/pnas.1700010114

10. Xu, J., Chmela, V., Green, N. et al. 2020 Selective prebiotic formation of RNA pyrimidine and DNA purine nucleosides. Nature 582, 60–66 (2020). Published: 03 June 2020. DOI: https://-doi.org/10.1038/s41586-020-2330-9 ■

'Central Dogma of Molecular Biology': Should 'Dogmas' and 'Cult Figures' Have Any Place in Science?

"The central dogma of molecular biology deals with the detailed residue-by-residue transfer of sequential information from DNA to protein via RNA. It states that such information is unidirectional from DNA to protein and cannot be transferred from protein to either protein or nucleic acid" (Crick F.,1970).

Stanley Miller performed experiments in 1952 and another in 1959 to understand and decipher the origins of life in the primordial earth environment and lived until 2007. During his time, DNA was understood to be an important biological molecule, actually the most important biological molecule in terms of informational polymer. However, Miller seemed to have totally missed explicitly making any mention of 'nucleic acid related informational molecule' in his works and thoughts.

One curious aspect about Miller's experiment is why he missed to look for nucleic acid informational polymer in early earth conditions, and only focused on amino acids? Is it because he did not use phosphate precursors, though phosphorus is likely to be present in primitive volcanic eruption conditions? Or did he assume that protein could only be the informational polymer and hence looked only for amino acids? Was he convinced that protein is the basis for origin of life and hence only looked for existence of amino acids in his experiment or the fact that proteins perform all the functions in the human body and are the basis of what we are phenotypically and hence are more important than nucleic acids, which he might have thought at that time?

There was a lot known about proteins and their

functionality 70 years ago and less about nucleic acid at that time. Since proteins are responsible for all biological reactions in the body, hence Miller thought that they should be information carrier; and hence looked for building blocks of protein only in his experiments. It is plausible that nucleic acid building blocks were also formed but were present in such trace amounts that couldn't be detected due to lack of sophisticated instrumentation.

DNA structure was revealed a year later in 1953, that proposed a double helical structure for DNA and talked about its replicative property. This gave birth to the famous 'Central Dogma of Molecular Biology' in 1970 by the celebrity scientist Francis Crick!1 And scientists got so tuned to and got convinced by the central dogma that they did not look back for nucleic acid precursors in primitive earth conditions.

The story does not seem to end with Miller; no one seems to have looked for nucleic acid precursors in primitive earth conditions for a very long time – something very surprising in this fast-moving phase of science. Though there are reports of synthesis of adenine in a prebiotic context2 but significant reports of prebiotic synthesis of nucleotide precursors were by Sutherland3 in 2009 and onward. In 2017 researchers4 simulated similar

reducing conditions as used by Miller and Urey to produce RNA nucleobases using electric discharges and high-power laser-driven plasma impacts.

If Miller had actually thought of protein as informational polymer then the question arises, "Is protein really an information polymer"? After nearly half a century of dominance of the 'central dogma', we get to see Koonin's paper5 of 2012 titled 'Does the central dogma still stand? The story of prion, a misfolded protein that causes disease, is a case in point. Why the misfolded prion protein in the body does not trigger immune response and/or is eliminated from the system? Instead, this misfolded protein starts making other proteins similar to it as "bad" as is the case in CZD disease. Why "good" proteins get guided/dictated by the other "bad" protein to be misfolded and why the cellular machinery does not stop that? What information does this misfolded protein has that is "transferred" to other similar proteins and they start acting erratically? Further, prions show extremely unusual properties, in particular extraordinary resistance to treatment that inactivates even the smallest nucleic acid molecules such as high-dose UV irradiation6. Prions can be destroyed by pre-heating at temperatures above 100°C in the presence of detergents followed by enzymatic treatment7.

Studies in yeast have shown that prion proteins possess a disordered prion-determining domain that triggers its conformational transition from good to "bad" protein8. The prion conformation forms spontaneously at a low frequency (on the order of 10-6)9 and switching to and from the prion state increases under stress conditions10. Mutants have been isolated in heterologous prion genes, with much higher frequency of prion formation11.

Do the above studies suggest that misfolded prion proteins pass on information to other proteins and may possibly back to DNA to trigger mutations in the prion genes? Genetic assimilation of prion-dependent phenotypic heredity suggests that it may be possible. However, till date, reverse translation (protein to DNA) has not been discovered and seems highly unlikely to ever be discovered due to the strong influence of central dogma and potential lack of funding for such endeavours.

However, it is conceivable that the underlying molecular mechanisms for the channel of information transfer from protein to DNA are completely different from the hypothetical reverse translation and may come to light at some point in time. It is difficult question to answer this but certainly free unfettered spirit of enquiry is the hallmark of science and getting married to a dogma or cult are anathema to science and has the potential to programme thinking of the scientific community.

References:

1. Crick F., 1970. Central Dogma of Molecular Biology. Nature 227, 561–563 (1970). DOI: https://-doi.org/10.1038/227561a0

2. McCollom TM., 2013. Miller-Urey and Beyond: What Have We Learned About Prebiotic Organic Synthesis Reactions in the Past 60 Years? Annual Review of Earth and Planetary Sciences. Vol. 41:207-229 (Volume publication date May 2013) First published online as a Review in Advance on March 7, 2013. DOI: https://doi.org/10.1146/annurev-earth-040610-133457

3. Powner, M., Gerland, B. & Sutherland, J., 2009. Synthesis of activated pyrimidine ribonucleotides in prebiotically plausible conditions. Nature 459, 239–242 (2009). https://doi.org/10.1038/nature08013

4. Ferus M, Pietrucci F, et al 2017. Formation of nucleobases in a Miller–Urey reducing atmosphere. PNAS April 25, 2017 114 (17) 4306-4311; first published April 10, 2017. DOI: https://-doi.org/10.1073/pnas.1700010114

5. Koonin, E.V. 2012. Does the central dogma still stand?.Biol Direct 7, 27 (2012). https://-doi.org/10.1186/1745-6150-7-27 ■

Barry's Half-Century of Saving lives in North Wales

AN AMBULANCE service stalwart is celebrating a half-century of saving lives in North Wales.

Fifty years ago today, on 08 June 1970, an 18-year-old Barry Davies from Drury, Flintshire, joined the ambulance service inspired by a childhood in the St John Ambulance Cadets.

Barry, now 68, began his career as an Ambulance Technician and has seen the organisation evolve from a small-scale local operation to Wales' national ambulance service.

He now works for the Trust's Non-Emergency Patient Transport Service, based in Wrexham.

Barry said: "I joined the St John Ambulance Cadets when I was 12, so going on to work for the ambulance service was a natural progression.

"Back then you were an 'ambulance man' and you did everything; the emergencies, the non-urgent hospital transfers and everything in between.

"Eventually, I went off to Wrenbury in Cheshire to do my Ambulance Technician training and that's how I spent my first 30 years in the service, based out of Flint Ambulance Station.

"The call that stands out in my mind is the time we delivered a baby in a card shop in Flint.

"You see everything in this job – nothing surprises me anymore!"

In 2007, Barry transferred to Mold Ambulance Station and was one of the first to join the Trust's new High Dependency Service, now known as the Urgent Care Service.

He later joined the Non-Emergency Patient Transport Service as an Ambulance Care Assistant having retired briefly and returned to the organisation.

Barry said: "I've watched our ambulance service evolve from Clwyd Ambulance Service to the North Wales Ambulance Service to the Welsh Ambulance Service it is today.

"When I look back, I feel immensely proud. It's absolutely flown by but I have such fond memories."

Barry's wife Lindsey is an Emergency Medical Technician based at Dobshill, Flintshire.

Lindsey, originally of Afonwen, also has 35 years' service under her belt – together the couple have served the people of North Wales for 85 years combined.

The pair enjoy gardening and travelling, and celebrated the New Year in South Africa.

Jason Killens, Chief Executive of the Welsh Ambulance Service, said: "Fifty years is an incredible length of service and we're so grateful and fortunate to have a colleague of long-standing like Barry.

"Barry has helped hundreds, if not thousands, of people over the years, many of whom would not be walking around Wales today if it were not for his skill and dedication.

"He's an extraordinary man who has committed his life to making sure people are taken care of."

Wayne Davies, the Trust's Locality Manager for Wrexham in Flintshire, said: "Barry is a well-liked and well-respected colleague, having served communities across North Wales for 50 years.

"Together with Lindsey, they are an incredible duo, and we thank them both for their service."

Joe Lewis, General Manager for the Non-Emergency Patient Transport Service in North Wales, added: "Congratulations Barry on a half-century of service.

"The people in North Wales are lucky to have you and long may you continue to serve them."

Barry will celebrate 50 years' service today with socially-distanced tea and cake with his colleagues on station.

"They're still making me bring the cakes though," he added. ■

Sun Pharma Presents Data, Offering Insights for Treating People with or at Risk of Skin Cancer

Sun Pharma has presented data on ODOMZO® (drug for treatment of skin cancer) and LEVULAN® KERASTICK® + BLU-U®, (for treating precancerous lesions) supporting safety and efficacy.

ODOMZO®

ODOMZO® (Sonidegib) was approved by FDA in July 2015. This was acquired by Sun Pharma from Novartis in Dec 2016 for $175 million upfront payment along with milestone payments.

It is a prescription medicine taken orally in the form of tablet to treat locally advanced basal cell carcinoma, that has resurfaced following surgery or radiation or that cannot be treated with surgery or radiation. This is an inhibitor of the Hedgehog signalling pathway. The Hedgehog (Hh) pathway is active during embryogenic development and is necessary for cell differentiation, tissue polarity, and stem cell maintenance. This pathway is silent in adult tissues under normal physiological conditions, however, aberrant Hh signalling activation has been implicated in the development and promotion of certain types of cancer, including basal cell carcinoma (BCC), medulloblastoma, and gastrointestinal cancers. Basal cell carcinoma and squamous cell carcinoma are most common forms of nonmelanoma skin cancers and affect more than three million Americans each year.

BOLT clinical trial for Odomzo, a double-blind, randomized, controlled, 42-month study evaluated ODOMZO 200 mg daily in 230 patients with locally

advanced basal cell carcinoma (laBCC) and metastatic basal cell carcinoma (mBCC). 2-year overall survival rates were found to be 93.2% (laBCC) and 69.3% (mBCC). The drug was safely tolerated.

LEVULAN® KERASTICK® + BLU-U®

This is only photodynamic therapy for precancerous skin lesions approved by the FDA (in July 1999) for use on the upper extremities to treat 'minimally to moderately' thick actinic keratoses of the face, scalp or upper extremities. These are precancerous skin growths that, if left untreated, may turn into squamous cell carcinoma. While only about 10 per cent of actinic keratoses become cancerous, the majority of squamous cell carcinoma cases start as actinic keratosis.

LEVULAN KERASTICK 20 % topical solution, plus blue light illumination is used to treat the lesions. After LEVULAN KERASTICK topical solution has been applied, the treatment site becomes photosensitive and patients should avoid exposure of the photosensitive treatment sites to sunlight or bright indoor light (e.g., examination lamps, operating room lamps, tanning beds, or lights at close proximity) for 40 hours.

In the clinical trials, there was a significant greater clearance of lesions (80.6%) in patients treated with this therapy compared to placebo (45.5%). In addition, there was a significant greater clearance of greater disease area in 80% of patients taking this therapy as compared to 40% with placebo. The therapy was well tolerated with no report of clinically significant adverse events.

Tildrakizumab for Treatment of Moderate-to-Severe Plaque Psoriasis: Could Sun Pharma's 'Ilumya' be a Better Option?

Tildrakizumab is being marketed by Sun Pharma under the trade name Ilumya, and has been approved by FDA in March 2018 after analysis of data from Phase III multi-centre, randomised, placebo-controlled clinical trials reSURFACE 1 and reSURFACE 2. Both studies achieved the primary endpoint of at least 75% of skin clearance as measured by PASI and PGA scores. The approval from European Commission and TGA, Australia came in September 2018. Based on the clinical and cost-effectiveness of Ilumya, NICE, UK has recommended the use of tildrakizumab in 2019 for the treatment of severe psoriasis.

Plaque psoriasis is an autoimmune inflammatory disease that inflicts nearly 125 million people across the world. Most common symptoms include red patchy lesions on parts of skin, including knees, elbow, scalp or lower back, that get inflamed and are itchy and painful. 80% of the people who contract the disease have mild to moderate symptoms while 20% have severe form the disease in which the plaques crack leading to bleeding and further discomfort. Psoriasis has significant social and economic implications for the patients suffering from the disease. The quality of life is impacted severely as patient's develop depression and suicidal tendencies due to 'normal' people maintaining social distancing from infected ones causing them to feel ashamed and leaving them in further distress.

A wide variety of treatments are available for psoriasis depending on the severity of

symptoms. It comprises of topical treatment using skin ointments, phototherapy, in which skin is exposed to UV light and systemic medication that includes chemical entities as well as biological entities such as antibodies.

The biological treatments in vogue for psoriasis include antibodies such as etanercept, adalimumab, infliximab, ustekinumab and tildrakizumab to name a few. These antibodies act by reducing inflammation by targeting the overactive cells of the host immune system. Biological treatments are often used in severe cases of psoriasis when patients do not respond to other treatments mentioned above.

Among the biological entities used for psoriasis treatment, tildrakizumab seems to be be the most effective in terms of reducing the symptoms as well as its costing. Clinical trial results have shown that tildrakizumab improves severe plaque psoriasis compared with placebo or etanercept with a marked improvement seen at 28 weeks. Moreover, tildrakizumab appears to be as effective as adalimumab and ustekinumab. With respect to costs, tildrakizumand is 18% more cost effective than adalimumab on a monthly basis leading to a significant cost reduction over a five-year period.

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Dexamethasone: Have Scientists Found Cure for Severely Ill COVID-19 Patients?

Low-cost dexamethasone reduces death by up to one third in hospitalised patients with severe respiratory complications of COVID-19

The scientists have been sceptic over the rationale for prolonged corticosteroid treatment in the Acute Respiratory Distress Syndrome (ARDS) caused by COVID-19. This has been studied by Villar et al1 recently where the authors talk about the scepticism based on evidence from only four small studies that suggests that patients are not being benefitted by steroid treatment2,3. However, studies from Wuhan, China4 and Itlay5 recommend use of steroids for ARDS caused by COVID-19. Now more concrete evidence has come from RECOVERY (Randomised Evaluation of COVid-19 thERapY) trial6 in favour of steroids by using dexamethasone for the treatment of severely ill COVID-19 patients in a randomised trial by a team of scientists from the University of Oxford, UK.

Over 11,500 patients have been enrolled from over 175 NHS hospitals in the UK to test various non-biological and biological drugs including hydroxychloroquine, anti-viral drugs and Tocilizumab. The trial which has been running since March 2020 has eventually seen a clear winner from the drugs used in a fight against COVID-19 and that is dexamethasone. Hydroxychloroquine was abandoned due to increased fatalities and heart problems while other drugs have been tried for COVID-19 as well, although with relatively less effectiveness as far as RECOVERY trial is concerned.

A total of 2104 patients were randomised to receive dexamethasone 6 mg once per day (either by mouth or by intravenous injection) for 10 days and were compared with 4321 patients who did not receive the drug. Among the patients who didn't receive the drug, 28-day mortality was highest in those who required ventilation (41%), intermediate in those patients who required oxygen only (25%), and lowest among those who did not require any respiratory intervention (13%). Dexamethasone reduced deaths by 33% in ventilated patients and by 20% in other patients receiving oxygen only. However, there was no benefit among those patients who did not require support for breathing.

Steroidal drugs have also been used in other studies involving COVID-19. In a study published by Lu et al7, 151 patients out of 244 patients were given a combination of antiviral drugs along with adjuvant corticosteroid treatment (median hydrocortisone-equivalent dosage 200 [range 100–800] mg/day). In this study, low survival rate (30%) was seen at 28 days with patients receiving such a high dosage of steroids compared to those who didn't (80%).

Dexamethasone has already been used to reduce inflammation in a range of other conditions. In case of COVID-19, dexamethasone seems to reduce the inflammation caused by the cytokine storm that develops as a consequence of

COVID-19 infection. Thus, this drug seems to be the miracle cure for high-risk COVID-19 patients that require hospitalisation. The treatment regimen of dexamethasone is up to 10 days and costs 5 pounds per patient. This drug is globally available and can be used to save lives of COVID-19 patients going forward.

More studies with dexamethasone need to be conducted across various countries and ethnic groups worldwide to establish its efficacy for COVID-19.

Have researchers finally found a low-cost, easily available, miracle cure for severe COVID-19 patients worldwide? The Oxford University group reports that low-cost dexamethasone reduces death by up to 33% in hospitalised patients with severe respiratory complications of COVID-19.

References:

1. Villar, J., Confalonieri M., et al 2020. Rationale for Prolonged Corticosteroid Treatment in the Acute Respiratory Distress Syndrome Caused by Coronavirus Disease 2019. Crit Care Explor. 2020 Apr; 2(4): e0111. Published online 2020 Apr 29. DOI: https:///doi.org/10.1097/CCE.0000000000000111

2. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet. 2020; 395:473–475

3. Delaney JW, Pinto R, Long J, et al. The influence of corticosteroid treatment on the outcome of influenza A(H1N1pdm09)-related critical illness. Crit Care. 2016; 20:75.

4. Shang L, Zhao J, Hu Y, et al. On the use of corticosteroids for 2019-nCoV pneumonia. Lancet. 2020; 395:683–684

5. Nicastri E, Petrosillo N, Bartoli TA, et al. National institute for the infectious diseases "L. Spallanzani", IRCCS. Recommendations for COVID-19 clinical management. Infect Dis Rep. 2020; 12:8543.

6. Oxford University News Release. 16 June 2020. Low-cost dexamethasone reduces death by up to one third in hospitalised patients with severe respiratory complications of COVID-19. Available online at https://www.recoverytrial.net/files/recovery_-dexamethasone_statement_160620_v2final.pdf Accessed on 16 June 2020.

7. Lu, X., Chen, T., Wang, Y. et al. Adjuvant corticosteroid therapy for critically ill patients with COVID-19. Crit Care 24, 241 (2020). Published 19 May 2020. DOI: https://doi.org/10.1186/s13054-020-02964-w ■

Bacterial Predator Could Help Reduce COVID-19 Deaths

A type of virus that preys on bacteria could be harnessed to combat bacterial infections in patients whose immune systems have been weakened by the SARS-CoV-2 virus that causes the COVID-19 disease, according to an expert at the University of Birmingham and the Cancer Registry of Norway.

Called bacteriophages, these viruses are harmless to humans and can be used to target and eliminate specific bacteria. They are of interest to scientists as a potential alternative to antibiotic treatments.

In a new systematic review, published in the journal Phage: Therapy, Applications and Research, two strategies are proposed, where bacteriophages could be used to treat bacterial infections in some patients with COVID-19.

In the first approach, bacteriophages would be used to target secondary bacterial infections in patients' respiratory systems. These secondary infections are a possible cause of the high mortality rate,

particularly among elderly patients. The aim is to use the bacteriophages to reduce the number of bacteria and limit their spread, giving the patients' immune systems more time to produce antibodies against SARS-CoV-2.

Dr Marcin Wojewodzic, a Marie Skłodowska-Curie Research Fellow in the School of Biosciences at the University of Birmingham and now researcher at the Cancer Registry of Norway, is the author of the study. He says: "By introducing bacteriophages, it may be possible to buy precious time for the patients' immune systems and it also offers a different, or complementary strategy to the standard antibiotic therapies."

Professor Martha R.J. Clokie, a Professor of Microbiology at the University of Leicester and Editor-in-Chief of PHAGE journal explains why this work is important: "In the same way that we are used to the concept of 'friendly bacteria' we can harness 'friendly viruses' or 'phages' to help us target and kill secondary bacterial infections caused by a weakened immune system following viral attack from viruses such as COVID-19".

Dr Antal Martinecz, an expert in computational pharmacology at the Arctic University of Norway who advised on the manuscript says: "This is not only a different strategy to the standard antibiotic therapies but, more importantly, it is exciting news relating to the problem of bacterial resistance itself."

In the second treatment strategy, the researcher suggests that synthetically altered bacteriophages could be used to manufacture antibodies against

Professor Martha R.J. Clokie's research focuses on the identification and development of bacteriophages that kill pathogens in an effort to develop new antimicrobials: "We could also exploit our knowledge of phages to engineer them to generate novel and inexpensive antibodies to target COVID-19. This clearly written article covers both aspects of phage biology and outlines how we might use these friendly viruses for good purpose."

Dr Wojewodzic is calling for clinical trials to test these two approaches.

"This pandemic has shown us the power viruses have to cause harm. However, by using beneficial viruses as an indirect weapon against the SARS-CoV-2 virus and other pathogens, we can harness that power for a positive purpose and use it to save lives. The beauty of nature is that while it can kill us, it can also come to our rescue." adds Dr Wojewodzic.

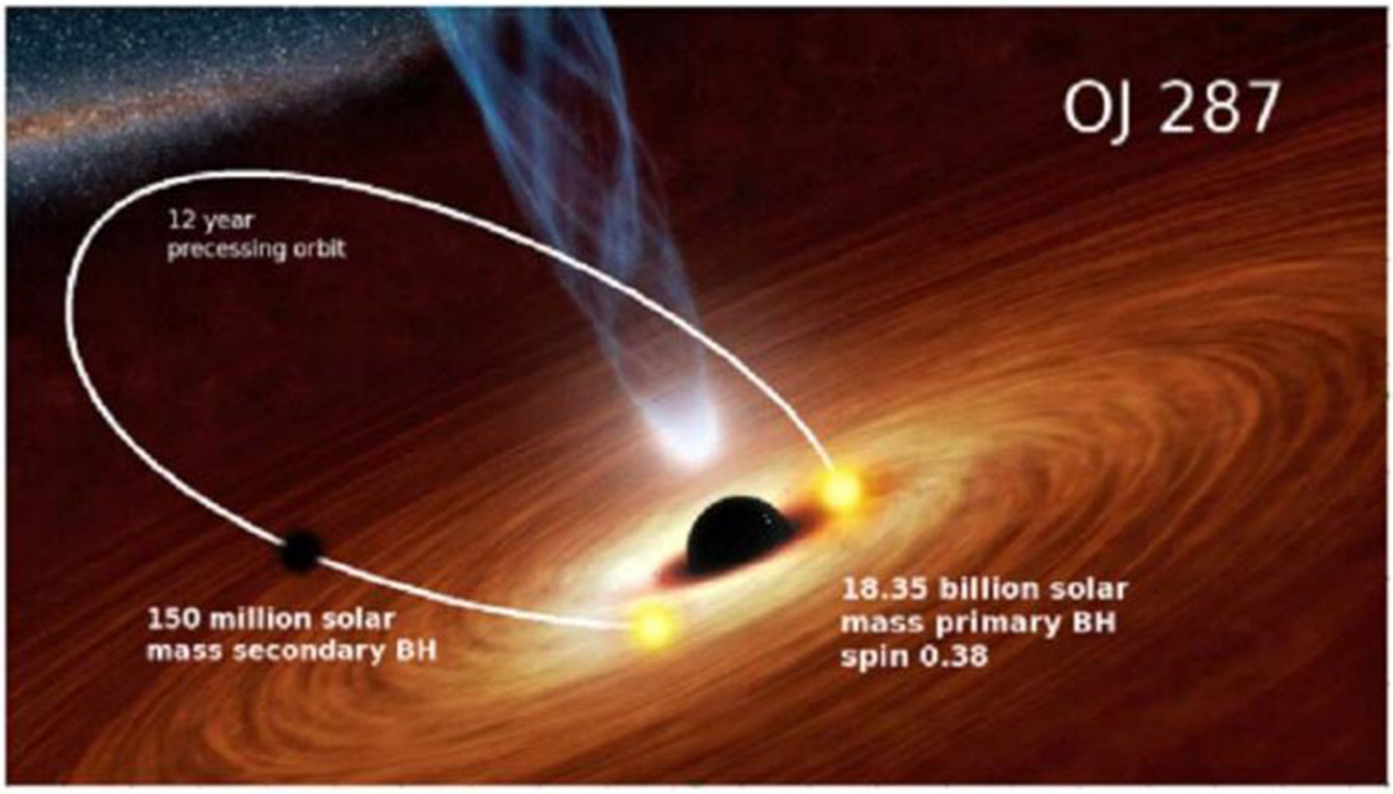
"It's clear that no single intervention will eliminate COVID-19. In order to make progress we need to approach the problem from as many different angles and disciplines as possible." concludes Dr Wojewodzic. ■

Flares from the Supermassive Binary Black Hole OJ 287 put constraint on the "No Hair Theorem"

NASA's infra-red observatory Spitzer has recently observed the flare from gigantic binary black hole system OJ 287, within the estimated time interval predicted by the model developed by astrophysicists. This observation has tested different aspects of General Relativity, the "No-hair theorem", and proved that OJ 287 is indeed a source of infra-red Gravitational Waves.

The OJ 287 galaxy, situated in Cancer constellation 3.5 billion light years away from Earth, has two black holes – the larger one with over 18 billion times the mass of the Sun and orbiting this is a smaller black hole with about 150 million times the solar mass, and they form a binary black hole system. While orbiting the larger one, the smaller black hole crashes through the enormous accretion disk of gas and dust surrounding its larger companion, creating a flash of light brighter than a trillion stars.

The smaller black hole collides with the accretion disk of the larger one twice in every twelve years. However, due to its irregular oblong orbit (called quasi-Keplarian in the mathematical terminology, as shown in the figure below), the flares can appear at different times – sometimes as little as one year apart; other times, as much as 10 years apart (1). Several attempts to model the orbit and predicting when flares would happen were unsuccessful until in 2010, when astrophysicists created a model that could predict their occurrence with an error of



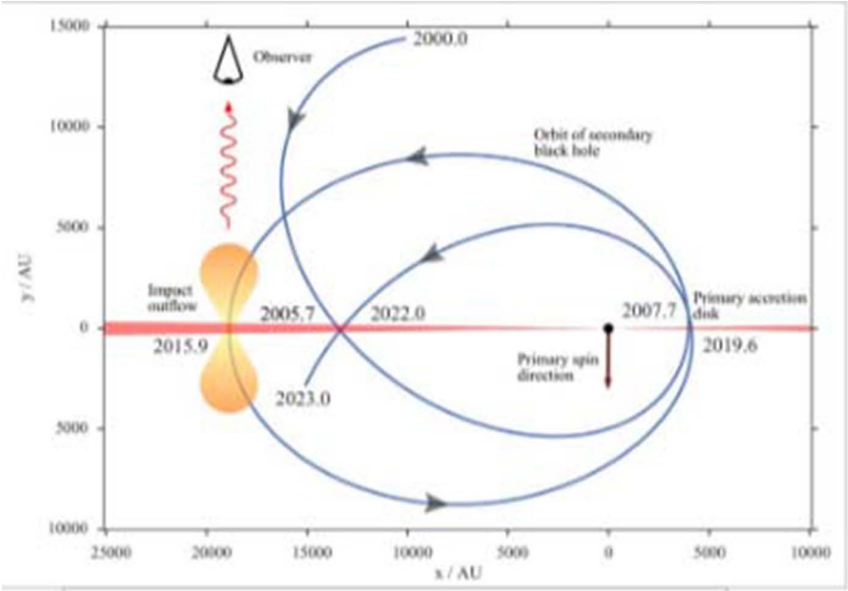
about one to three weeks. The accuracy of the model was demonstrated by predicting the appearance of a flare in December 2015 to within three weeks.

Another important piece of information that went into the making of a successful theory of binary black hole system OJ 287 is the fact that supermassive black holes can be sources of gravitational waves – which has been established after the experimental observation of the gravitational waves in 2016, produced during the merging of two supermassive black holes. OJ 287 has been predicted to be the source of infra-red gravitational waves (2).

In 2018, a group of astrophysicists provided an even more detailed model, and claimed to be able to predict the timing of future flares to within few hours (3). According to this model, the next flare would occur on July 31, 2019 and the time was predicted with an error of 4.4 hours.

It also predicted the brightness of the impact-induced flare to take place during that event. The event was captured and confirmed by NASA's Spitzer Space Telescope (4), which retired in January 2020. To observe the predicted event, Spitzer was our only hope since this flare could not be seen by any other telescope on the ground or in Earth's orbit, as the Sun was in Cancer constellation with OJ 287 and Earth being on opposite sides of it. This observation also proved that OJ 287 emits gravitational waves in the infra-red wavelength, as predicted. According to this proposed theory the impact-induced flare from OJ 287 is expected to take place in 2022.

The observations of these flares put a constraint on the "No hair theorem" (5,6) which states that while black holes don't have true surfaces, there is a boundary around them beyond which nothing – not even light – can escape. This boundary is called the event horizon. This theorem also postulates that the matter which forms a black-hole or is



falling into it "disappears" behind the black hole event horizon and is therefore permanently inaccessible to external observers, suggesting that black holes have "no hair". One immediate consequence of the theorem is that the black holes can be characterized completely with their mass, electric charge and intrinsic spin. According to some scientists, this outer edge of the black-hole, i.e. the event horizon, could be bumpy or irregular, thus contradicting the "No hair theorem". However, if one has to prove the correctness of the "No hair theorem", the only plausible explanation is that the uneven mass distribution of the large black-hole would distort the space around it in such a manner that it would lead to a change of path of the smaller black hole, and in turn change the timing of the black hole's collision with the accretion disk on that particular orbit, thus causing a change in the time of appearance of the flares observed.

As can be expected, black holes are hard to probe. Hence, as we move forward, many more experimental observations regarding black hole interactions, with the surroundings as well as with other black holes, are to be studied before one can confirm the validity of the "No hair theorem".

References:

1. Valtonen V., Zola S., et al. 2016, "Primary black hole spin in OJ287 as determined by the General Relativity centenary flare", Astrophys. J. Lett. 819 (2016) no.2, L37. DOI: https://-doi.org/10.3847/2041-8205/819/2/L37

2. Abbott BP., et al. 2016. (LIGO Scientific Collaboration and Virgo Collaboration), "Observation of Gravitational Waves from a Binary Black Hole Merger", Phys. Rev. Lett. 116, 061102 (2016). DOI: https://doi.org/10.1103/PhysRev-Lett.116.061102

3. Dey L., Valtonen MJ., Gopakumar A. et al 2018. "Authenticating the Presence of a Relativistic Massive Black Hole Binary in OJ 287 Using Its General Relativity Centenary Flare: Improved Orbital Parameters", Astrophys. J. 866, 11 (2018). DOI: https://-doi.org/10.3847/1538-4357/aadd95

4. Laine S., Dey L., et al 2020. "Spitzer Observations of the Predicted Eddington Flare from Blazar OJ 287". Astrophysical Journal Letters, vol. 894, No. 1 (2020). DOI: https://-doi.org/10.3847/2041-8213/ab79a4

5. Gürlebeck, N., 2015. "No-Hair Theorem for Black Holes in Astrophysical Environments", Physical Review Letters 114, 151102 (2015). DOI: https://-doi.org/10.1103/PhysRevLett.114.151102

6. Hawking Stephen W., et al 2016. Soft Hair on Black Holes. https://arxiv.org/pdf/1601.00921.pdf ▪