Infectious Pathogens and Cancer: The Emerging Evidence

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WHO, 1997: “Up to 84% of cases of some cancers are attributable to viruses, bacteria, and parasites”

“A growing body of research suggests that a number of viruses, bacteria, and parasites cause cancer in humans, thus providing new possibilities for treatment and prevention of cancer. In 1997, the World Health Organization estimated that up to 84% of cases of some cancers are attributable to viruses, bacteria and parasites, and that more than 1.5 million (15%) new cases each year could be avoided by preventing the infectious disease associated with them. … The pathogenic mechanisms by which infectious agents cause cancer have not been resolved but they appear to be diverse. … This finding not only suggests a causal role but that treatment of a bacterial infection can actually result in regression of cancer.”

Cassell, GH. Infectious Causes of Chronic Inflammatory Diseases and Cancer Emerging Infectious Diseases. National Center for Infectious Diseases. Centers for Disease Control and Prevention, Atlanta, GA.

“... since the discovery of links between H. pylori and gastric lymphomas and adenocarcinomas, and HPV-induced neoplasias from mouth to anal domains, chronic infections have provided a model to explain the transit of a benign cell into a malignant cell.”

Alan B. MacDonald, M.D., Fellow, College of American Pathologists, January 2016

Infectious Pathogens and Cancer: The Emerging Evidence

1. Stealth bacteria involvement
2. Viral involvement
3. Indirect involvement
Infectious Pathogens and Cancer: The Emerging Evidence

1. Stealth bacteria involvement
   - Borrelia
   - Bartonella
   - Babesia
   - Chlamydia pneumoniae
   - Mycoplasma
   - Chlamydia trachomatis
   - Ehrlichia
   - Toxoplasma

2. Viral involvement

3. Indirect involvement
Borrelia and non-Hodgkin/mantle cell lymphoma

“Our observations suggest a previously unreported association between *B burgdorferi* infection and risk of mantle cell lymphoma.”

“Moreover, regression of lymphomas upon treatment of the Borrelia infection has also been reported”
Borrelia in Glioblastoma Multiformae

Glioblastoma Multiformae Brain Biopsies - Formalin fixed- with Immunohistochemical Full Pam=nelPane Panel evaluation and Confirmation of Diagnosis by neuropathologist- ---
Images (3 per case) of FISH DNA probe for detection of Burgdorferi Borrelia DNA with DNA probes specific for gene of Inner cell membrane of Burgdorferi Borrelia Gene bbo 0740- Validated DNA probe and all Controls acceptable

"In the case of neurons, glial cells and Borrelia, there is evidence from co-incubation of cells in tissue culture with living Borrelia in pure cultures that Borrelia first binds to the tissue cultured cells, and then, stepwise, inserts the entire spirochete into the cytoplasm and then into the nucleus of glial cells. Liposomes from Borrelia's outer surface membrane contain DNA. Transmission electron micrographs have imaged the transit of Borrelia liposomes from the external cellular milieu, to penetrate the cytoplasm of eukaryotic cells, and next to penetrate the nucleus."

Bartonella is able to produce tumours

Current Knowledge of Bartonella Species

M. Maurin, R. Birtles, D. Raoult*

Bartonella species are now considered emerging pathogens. Of the 11 currently recognized species, four have been implicated in human disease, although only two have been encountered in Europe. Bartonella quintana infections are now being diagnosed among the urban homeless and deprived, manifesting as trench fever, and Bartonella henselae has been shown to be the causative agent of cat scratch disease. Both species also cause a variety of HIV-associated infections, including bacillary angiomatosis. However, perhaps the most significant presentation of bartonellae infection is culture-negative endocarditis. The epidemiologies of Bartonella infections are poorly understood; most Bartonella henselae infections are probably acquired from infected cats, either directly by contact with a cat or indirectly via fleas. No animal reservoir has been implicated for Bartonella quintana; however, infection can be transmitted via the human body louse. Diagnosis of Bartonella infections can be made using histological or microbiological methods. The demonstration of specific antibodies may be useful in some instances, although certainly not in all. Cultivation of Bartonella is difficult, as the bacteria are extremely fastidious. Polymerase chain reaction-based or immunological methods for the detection of bartonellae in infected tissues have proven useful. Clinical relapse is often associated with Bartonella infections despite a wide range of prescribed regimens. Only aminoglycosides display in vitro bactericidal activity against intracellular Bartonella species; therefore, they are recommended for treatment of Bartonella infections.

Human infections due to Bartonella species are widely considered emerging diseases. They include long-recognized diseases such as Carrión's disease (classical bartonellosis), trench fever, and cat-scratch disease and newer clinical manifestations such as bacillary angiomatosis, peliosis hepatitis, septicemia, endocarditis, chronic lymphadenopathy, and neurologic disorders. New molecular biology techniques, mainly based on 16S rRNA gene amplification and analysis, have allowed recognition of the role of Bartonella (formerly Rochalimaea) species in a number of these  


"Bartonellae are the only known bacteria with the ability to produce angiogenic tumors in humans"
Bartonella: angioproliferative lesions

In Vitro Model of Bartonella henselae-Induced Angiogenesis

James E. Kirby

ABSTRACT

Bartonella henselae is a gram-negative pathogen that causes angiogenesis. Here, I establish in vitro models to study Bartonella-induced blood vessel formation. I found that B. henselae induces long-term endothelial survival and tubular differentiation within type I collagen matrix.

Bartonella henselae is an emerging bacterial pathogen that causes disease, endocarditis, and angioproliferative lesions in AIDS patients. Angioproliferative lesions are the most unique and defining feature of proliferating endothelial cells, these aggregates of immature vascular abnormal form of angiogenesis. They differ from the less exuberant stimulation by vascular endothelial growth factor (VEGF), a critical producer by tumors or introduced experimentally.

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC529148/figure/f2/
Bartonella and MGUS (Monoclonal Gammopathy of Undetermined Significance)

Transient monoclonal gammopathy in a patient with Bartonella quintana endocarditis.

Sève P¹, Turner R, Stankovic K, Perard L, Brousse C.

Abstract
Monoclonal gammopathy has been reported rarely in association with infectious diseases. Viral infection has been the most frequently reported. We report a case of Bartonella quintana endocarditis in a 45-year-old homeless male associated with a monoclonal IgG kappa gammopathy. The gammopathy disappeared after 8 months of antibiotics while the Bartonella antibody titre was decreasing. This correlation suggests a causative role for B. quintana for the monoclonal gammopathy. To the best of our knowledge, this is the first report of monoclonal gammopathy in the course of B. quintana infection.

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PmID: 16432867 DOI: 10.1002/ajh.20499

“This correlation suggests a causative role for B. quintana for the monoclonal gammopathy.”

“The gammopathy disappeared after 8 months of antibiotics”
Bartonella henselae in breast cancer

"An acute inflammatory reaction triggered by the Bartonella infected endothelium may be crucial for initiating the chronic inflammation in inflammatory breast cancer patients and the rapid spread of tumor cells."

"Interestingly, the majority of case patients in the study had underlying B-cell lymphoma"
Chlamydia pneumoniae associated with lung cancer

“CHSP-60 seropositivity and elevated antibody titers were associated with significantly increased risk for subsequent lung cancer, supporting an etiologic role for C. pneumoniae infection in lung carcinogenesis.”

“Higher titre may be a better predictor of lung cancer risk”

Source: http://cebp.aacrjournals.org/content/19/6/1498.long; https://www.ncbi.nlm.nih.gov/pubmed/21194924
Chlamydia pneumoniae in prostate cancer

Source: https://www.prostatitis.org/a212000.html

“100% of the prostate biopsies (N. 10 patients) were positive, demonstrating the presence of the micro-organism inside the prostate gland both in prostatitis, benign prostate hyperplasia and prostate cancer patients.”
High level of Mycoplasma in various cancers

There was high correlation between mycoplasma infection and different cancers, which suggests the possibility of an association between the two.

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4723534/
"This study by Barykova et al. ([7]) is the latest of several that indicate a strong link between mycoplasma species and prostate cancer."

Abstract

The origin of chronic inflammation preceding the development of prostate cancer (PCa) remains unknown. We investigated possible involvement of mycoplasma infection in PCa by screening prostate biopsies from two groups of Russian men undergoing PCa diagnosis. *M. hominis* was detected by standard PCR in 15% of the 125 patients in the first group and by quantitative real-time PCR in 37.4% of the 123 men in the second group. In both groups, stratification of patients according to diagnosis showed that *M. hominis* was present at three times higher frequency in patients with PCa than in those with benign prostatic hyperplasia. No *M. hominis* was detected in the prostates of 27 men without detectable prostate disease. In addition, PCa-positive men had higher titers of antibodies against *M. hominis* and average PSA levels were higher in *M. hominis*-positive men. These data, together with previous observations linking mycoplasma infection with cell transformation, genomic instability and resistance to apoptosis, suggest that *M. hominis* infection may be involved in PCa development and may, therefore, be a potential PCa marker and/or target for improved prevention and treatment of this disease.
Mycoplasma infection transforms normal lung cells and induces bone morphogenetic protein 2 expression by post-transcriptional mechanisms.

Jiang S1, Zhang S, Langenfeld J, Lo SC, Rogers MB.

Abstract
Bone morphogenetic protein 2 (BMP2) is an essential growth factor and morphogen, whose pathological overexpression influences development and physiology. We present the novel finding that mycoplasma infection triggered BMP2 protein in BEAS-2B cells (immortalized human bronchial epithelial cells), which normally do not produce BMP2 in A549 cells (lung adenocarcinoma cells). Indeed, mycoplasma is as strong an expander of BMP2 production as retinoic acid. Second, we showed that post-transcriptional mechanisms including regulatory RNA mechanisms, contributed to the increased BMP2 expression in mycoplasma-infected cells. Furthermore, we identified AS1441 that binds the post-transcriptional regulator nucleolin induced BMP2 exclusively in infected BEAS-2B cells transformed by chronic mycoplasma infection, as demonstrated by a transfection assay. These findings have important implications regarding the effects of mycoplasma on BMP2-regulated lung differentiation, and apoptosis.
Detection of mycoplasma infection in circulating tumor cells in patients with hepatocellular carcinoma.


Abstract

Many studies have shown that persistent infections of bacteria promote carcinogenesis and metastasis. Infectious agents and their products can modulate cancer progression through the induction of host inflammatory and immune responses. The presence of circulating tumor cells (CTCs) is considered as an important indicator in the metastatic cascade. We unintentionally produced a monoclonal antibody (MAb) CA27 against the mycoplasma p37 protein in mycoplasma-infected cancer cells during the searching process of novel surface markers of CTCs. Mycoplasma-infected cells were enriched by CA27-conjugated magnetic beads in the peripheral blood mononuclear cells in patients with hepatocellular carcinoma (HCC) and analyzed by confocal microscopy with anti-CD45 and CA27 antibodies. CD45-negative and CA27-positive cells were readily detected in three out of seven patients (range 12-30/8.5 ml blood), indicating that they are mycoplasma-infected circulating epithelial cells. CA27-positive cells had larger size than CD45-positive hematological lineage cells, high nuclear to cytoplasmic ratios and irregular nuclear morphology, which identified them as CTCs. The results show for the first time the existence of mycoplasma-infected CTCs in patients with HCC and suggest a possible correlation between mycoplasma infection and the development of cancer metastasis.

KEYWORDS: Circulating tumor cell; Hepatocellular carcinoma; Metastasis; Monoclonal antibody.
Chlamydia trachomatis blocks apoptosis by destroying the p53 tumour suppressor gene

A research team at the Max Planck Institute for Infection Biology in Berlin has now observed the breakdown of an important endogenous protective factor in the course of chlamydial infection. **By activating the destruction of p53 protein, the bacterium blocks a key protective mechanism of infected cells, the initiation of programmed cell death. This protective function of p53 is also impaired in many forms of cancer.**

*Chlamydia infection promotes host DNA damage and proliferation but impairs the DNA damage response. Chumduri et al. Cell host & microbe, Vol: 13, Issue: 6, Page: 746-58, 2013*

Chlamydia trachomatis is associated with a greater risk of invasive cervical cancer

“This study, based on data from 1,238 case and 1,100 control participants in 7 countries worldwide, shows that C. trachomatis serum antibodies were associated with a 1.8-fold increased risk of squamous cell invasive cervical cancer.”

Ehrlichia associated with myelodysplastic disease and leukaemia

Could ehrlichial infection cause some of the changes associated with leukemia, myelodysplastic diseases and autoimmune disorders, and offer antibiotic treatment options?

Charles A. Kallick, Daniel A. Friedman, Mramba B. A. Nyindo

Abstract

We hypothesize that a large group of medical conditions of unknown etiology including leukemia, multiple myeloma, myelodysplastic and autoimmune disorders, may be associated with or caused by an obscure group of intracellular obligate parasitic bacteria named Ehrlichia/Anaplasma (EA). Ensconced in the stem cells of the bone marrow, EA may disrupt the normal development and function of many of the cells of immunity, manifesting itself as different syndromes. Recent studies of the activity of EA suggest direct effects on the immune system consistent with the manifestations of leukemia. We reference here three leukemia patients with direct or indirect evidence of EA infection. Moreover, EA have been
**Toxoplasma may increase the risk of brain cancer**

"We predicted that T. gondii could increase the risk of brain cancer because it is a long-lived parasite that encysts in the brain, where it provokes inflammation and inhibits apoptosis. …

Infection with T. gondii was associated with a 1.8-fold increase in the risk of brain cancers across the range of T. gondii prevalence in our dataset (4-67%)."
Toxoplasmosis higher in patients with solid organ tumors

Toxoplasmosis: an overlooked infection in cancer patients


Annals of Oncology, Volume 27, Issue suppl_6, 1 October 2016, 1383P,
https://doi.org/10.1093/annonc/mdw387.20
Published: 11 October 2016

Background: Toxoplasmosis is a widespread disease caused by the Apicomplexan, coccidian protozoan Toxoplasma gondii (T. gondii). Human prevalence rates for toxoplasmosis vary greatly in different parts of the world ranging from 0% in North Alaska and Canada to 94% in Costa Rica and Guatemala. Once the host acquires the infection by ingestion, T. gondii crosses the intestinal epithelium, disseminates into the deep tissues and traverses biological barriers to reach sites where it causes severe pathology. Normally, the immune response efficiently prevents the dissemination of the parasite. In immunocompromised hosts, however, such reactivation may be more frequent, leading to a massive and potentially fatal recrudescence. Studies of prevalence of Toxoplasmosis in patients with neoplasms are scarce. This report represents the first prevalence study of Toxoplasmosis in cancer patients in Egypt.

Methods: Blood samples were collected from 150 immunocompromised patients having different types of malignancies as well as 50 immunocompetent individuals as a control group, to assess the seroprevalence of anti-T. gondii antibodies. The “CTK biotech Onsite Toxo IgG/IgM Rapid Test Cassettes” was used according to the manufacturer’s enclosed manual for the detection of infection.

“Among cancer patients, prevalence of T. gondii was significantly higher (20% & 4% for IgG and IgM respectively) compared with controls (8% and 2%) (p = 0.003). Toxoplasmosis was higher in patients having solid organ tumors (24%) than in patients with haematological malignancies (12%) (p = 0.06).”
Which bacterial tests to consider, in which cancers?

<table>
<thead>
<tr>
<th>Type of cancer</th>
<th>Bacterial tests to consider</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoma</td>
<td>Borrelia (Elispot/Seraspot), Babesia (Elispot), Ehrlichia/Anaplasma (Elispot/IgG, IgM)</td>
</tr>
<tr>
<td>Monoclonal gammopathy</td>
<td>Bartonella (Elispot)</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>Ehrlichia/Anaplasma (Elispot/ IgG, IgM)</td>
</tr>
<tr>
<td></td>
<td>Coxiella (Q fever) (IgG, IgM)</td>
</tr>
<tr>
<td>Glioma/brain cancers</td>
<td>Borrelia (Elispot/Seraspot)</td>
</tr>
<tr>
<td></td>
<td>Mycoplasma (Elispot/IgG, IgA)</td>
</tr>
<tr>
<td></td>
<td>Toxoplasma (IgG, IgM)</td>
</tr>
<tr>
<td>Angiogenic tumours</td>
<td>Bartonella (Elispot)</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>Chlamydia pneumoniae (Elispot/IgG, IgA), Mycoplasma (Elispot/IgG, IgA)</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>Chlamydia pneumoniae (Elispot/IgG, IgA), Mycoplasma (Elispot/IgG, IgA)</td>
</tr>
<tr>
<td>Oesophageal</td>
<td>Mycoplasma (Elispot/IgG, IgA)</td>
</tr>
<tr>
<td>Breast</td>
<td>Mycoplasma (Elispot/IgG, IgA)</td>
</tr>
<tr>
<td></td>
<td>Bartonella (Elispot)</td>
</tr>
<tr>
<td>Metastases</td>
<td>Mycoplasma (Elispot/IgG, IgA)</td>
</tr>
<tr>
<td>Cervical cancer, downregulation of p53</td>
<td>Chlamydia trachomatis (Elispot/IgG, IgA)</td>
</tr>
<tr>
<td>Solid tumours (if cat owner/contact with cats)</td>
<td>Toxoplasma</td>
</tr>
<tr>
<td>General</td>
<td>CD3/CD57+</td>
</tr>
</tbody>
</table>
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1. Stealth bacteria involvement

2. Viral involvement
   - Epstein Barr Virus
   - Cytomegalovirus
   - HHV6
   - Herpes Simplex Virus 1 & 2

3. Indirect involvement
Epstein Barr virus

“Epstein-Barr virus (EBV) is a tumorigenic herpes virus, which is associated with several human hematologic neoplasias such as Burkitt lymphoma, Hodgkin disease, and posttransplantation lymphoproliferative disease (PTLD)”

B-Cell Non-Hodgkin’s Lymphoma: EBV/CMV


History of the discovery of EBV points to its tumorigenic origin

“The fact that the geographical distribution of Burkitt’s lymphoma (BL) overlapped that of several mosquito-borne diseases suggested the possibility that the disease was transmittable. Burkitt gave several talks about his findings on a visit to London, and Anthony Epstein, a virologist interested in tumor viruses, was present. He had Burkitt send him samples of the tumors and was able to detect a herpes-like virus by electron microscopy.”

Source: Epstein-Barr Virus and Cytomegalovirus infections Alex Tselis
EBV/CMV and tumours

“The role of EBV was then established in a number of tumors”

Source: Epstein-Barr Virus and Cytomegalovirus infections Alex Tselis
EBV: Latency antigens associated with various types of cancer

<table>
<thead>
<tr>
<th>Latency type</th>
<th>Latency antigens</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBER</td>
<td>EBNA-1</td>
</tr>
<tr>
<td>1</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>+</td>
</tr>
<tr>
<td>Other</td>
<td>+</td>
</tr>
</tbody>
</table>

Different latencies associated with Burkitt’s lymphoma, nasopharyngeal carcinoma, Hodgkin’s disease, lymphoproliferative disease

Source: Epstein-Barr Virus and Cytomegalovirus infections Alex Tselis

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Scientists reveal how a common virus triggers blood cancer

Scientists at the University of Sussex, trying to uncover how the common Epstein-Barr virus causes blood cancer in adults and children, have discovered how the virus takes control of two genes involved in cancer development so it can switch them on or off.

The research team, led by Professor Michelle West, set out to determine how the Epstein-Barr virus controls two genes: MYC, a gene known to drive cancer development when it is altered or switched on at high level and BCL2L11, a gene which normally triggers cell death to prevent cancer, but can be turned off by the virus.

With thanks to funding from the blood cancer charity Bloodwise, the scientists discovered that the virus controls the MYC and BCL2L11 genes by hijacking “enhancer” DNA regions which are situated far away from the genes. These enhancers act as ‘control centres’ and are able to contact and control genes from long distances by the looping out of the intervening stretches of DNA.

Professor West’s team found that Epstein-Barr virus turns on the MYC gene by increasing contacts between a specific set of enhancers and the gene. The scientists believe this may explain how the virus causes the changes to the MYC gene that are found in Burkitt’s lymphoma.

The team also discovered new enhancers which control the BCL2L11 gene. In this case, they found that Epstein-Barr virus stops these control centres from contacting the gene. Encouragingly the team have discovered that this blocking effect can be reversed by using a specific drug - paving the way for new treatments.

Professor West said: “This is a key step towards uncovering how this common virus which, affects thousands of people every year, causes blood cancer. It is now important to carry out further studies to confirm our findings and to tell us more about how the virus drives lymphoma development and how we can target the virus with drugs.”

Dr Alasdair Rankin, Research Director at Bloodwise, said: “This is exciting progress, but we were never sure of the exact mechanisms. These findings show how Epstein-Barr virus hijacks genes that control cancer growth.

“By mapping out the complex genetic interactions that help lymphoma cells grow and survive, this research can guide the design of new treatments to target the disease. It may also help to identify those drugs currently used to treat other diseases that could be effective in treating these types of lymphoma.”
HHV6 and Hodgkin’s disease

“Patients with Hodgkin's disease (HD) frequently show elevated serum titers against human herpesvirus-6 (HHV-6) and their tissues contain significantly increased numbers of cells with HHV-6 DNA.”

Herpes viruses and blood cancers: tests suggested

1. EBV EliSpot
2. EBV IgG/IgM, anti-EBNA antibodies and early antigen
3. CMV IgG/IgM
4. CMV EliSpot
5. HHV6 IgG/IgM
6. CD3/CD57+ cells
Link between HSV1 and oral cancer well established; HSV2 and cervical cancer more equivocal

“The present study clearly indicates that quantitative estimation of IgG antibody against HSV-1 in cancer/precancer patients will give the clue in the etiology of cancer or precancer.”
Infectious Pathogens and Cancer: The Emerging Evidence

1. Bacterial involvement

2. Viral involvement

3. Indirect involvement:
   .... these stealth pathogens indirectly cause a conducive environment to multiple diseases, including cancer ...
Borrelia – and other intracellular bacterial/viral infections – cause mitochondrial dysfunction

"The results suggest that oxidative stress and interrupted intracellular communication may ultimately contribute to a condition of mitochondrial dysfunction in the immune cells of Lyme borreliosis patients." …

... potentially contributing to cancer, as we have heard from other speakers today

**Indirect links: unfortunately a perfect physiological storm**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Borrelia</strong></td>
<td>Oxidative stress causes damage to DNA, proteins and lipids&lt;br&gt;Utilises host purines (ATP)&lt;br&gt;Depletes cell and mitochondrial membranes&lt;br&gt;Upregulates mitochondrial superoxide levels&lt;br&gt;This together can cause huge inflammation</td>
</tr>
<tr>
<td><strong>Babesia</strong></td>
<td>Infects erythrocytes = can cause <strong>haemolysis</strong> and intravascular coagulation = <strong>hypoxia</strong>&lt;br&gt;Thrombocytopenia = <strong>immunosuppression</strong></td>
</tr>
<tr>
<td><strong>Bartonella</strong></td>
<td>Parasitised erythrocytes sequestered by the spleen = immunosuppression</td>
</tr>
<tr>
<td><strong>Mycoplasma</strong></td>
<td>Prefers low-oxygen environments, stimulates ROS, which causes&lt;br&gt;<strong>damage to cell membranes – membrane potential is lost</strong></td>
</tr>
<tr>
<td><strong>Ehrlichia</strong></td>
<td>Infects leukocytes = immunosuppression</td>
</tr>
<tr>
<td><strong>Anaplasma</strong></td>
<td>Infects granulocytes = immunosuppression</td>
</tr>
<tr>
<td><strong>All these stealth pathogens ...</strong></td>
<td>... cause inflammation, as inflammation breaks down tissues and allows the bacteria to gain access to the host’s resources&lt;br&gt;Interfere with/disable the host’s immune system, <strong>upregulate cytokines, trigger ROS/RNS</strong>&lt;br&gt;... <strong>shift host’s immune response from Th1 (intracellular) towards Th2 (extracellular)</strong> to distract attention from their location – <strong>but Th2 is conducive to cancer</strong></td>
</tr>
</tbody>
</table>

*Sources: All available on request*
Thank you very much for your attention!

For tests, please go to
www.aonm.org
https://aonm.org/arminlabs

or call the AONM helpline
on 0333 121 0305