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Biomedical Journal

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## Highlights

# The best protection is early detection Fostering timely and accurate screening

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### ARTICLE INFO

#### Article history:

Available online 15 January 2022

#### Keywords:

Tuberculosis

Cancer

Transplant

Circulating tumor cells

Diabetic retinopathy

### ABSTRACT

This current special issue of the *Biomedical Journal* provides insights in various cancer forms, and possible ways of prognostic and predictive screening. In detail we learn about lung cancer and tissue samples from ground glass opacifications, liquid biopsy through circulating tumor cells in colon cancer, transcription factor analysis in cervical cancer, and long non-coding RNAs in breast and lung cancer. A prognosis factor in individuals with acute myeloid leukemia and a rare fungal infection are determined. Challenges surrounding transplantation are elucidated, a potential biomarker for allograft dysfunction is presented, as well as a mean to save beta cells after islet transplantation. We get to know more about drug resistance in transplant recipients with tuberculosis, and also in the case of *Helicobacter pylori* infection. Lastly, the possibilities of cardiac shock wave therapy in simultaneous artery and renal disease is explored, we are presented with genetic factors contributing to cancer risk in arseniasis areas, and protocol recommendations for the optimal reproducibility of bladder volume in prostate cancer treatment. Three markers for detecting stages of diabetic retinopathy are covered, as well as a way to mitigate effects of lungworm secretions. Finally we get to see a novel approach for acupuncture needle material, and two management approaches for a form of skeletal malocclusion.

## Spotlight

Since the year 2000 the World Cancer Day (WCD) takes place on 4th February.<sup>1</sup> It is an initiative of the Union for International Cancer Control (UICC), a NGO brought to life in 1933 with the goal to promote the fight against cancer through research, therapy and social activities.<sup>2</sup> The organization predicts the number of cancer deaths to increase to 13.2

million per year by 2030 if no major efforts are undertaken like for instance increased governmental support and funding for cancer prevention, detection and treatment programs.<sup>3</sup>

### Shades of Grey

Lung cancer (LC) was the most common cancer death in 2020 with 1.8 million cases.<sup>4</sup> There are two main types of LC, small cell LC (SCLC) is considered to be more aggressive in contrast

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Peer review under responsibility of Chang Gung University.

<sup>1</sup> <https://www.worldcancerday.org/our-story>, last access 2022-01-05.

<sup>2</sup> <https://www.uicc.org/who-we-are/about-uicc/history-uicc>, last access 2022-01-05.

<sup>3</sup> <https://www.uicc.org/what-we-do/convening/world-cancer-day/why-world-cancer-day-matters>, last access 2022-01-05.

<sup>4</sup> <https://www.who.int/news-room/fact-sheets/detail/cancer>, last access 2022-01-03.

<https://doi.org/10.1016/j.bj.2022.01.010>

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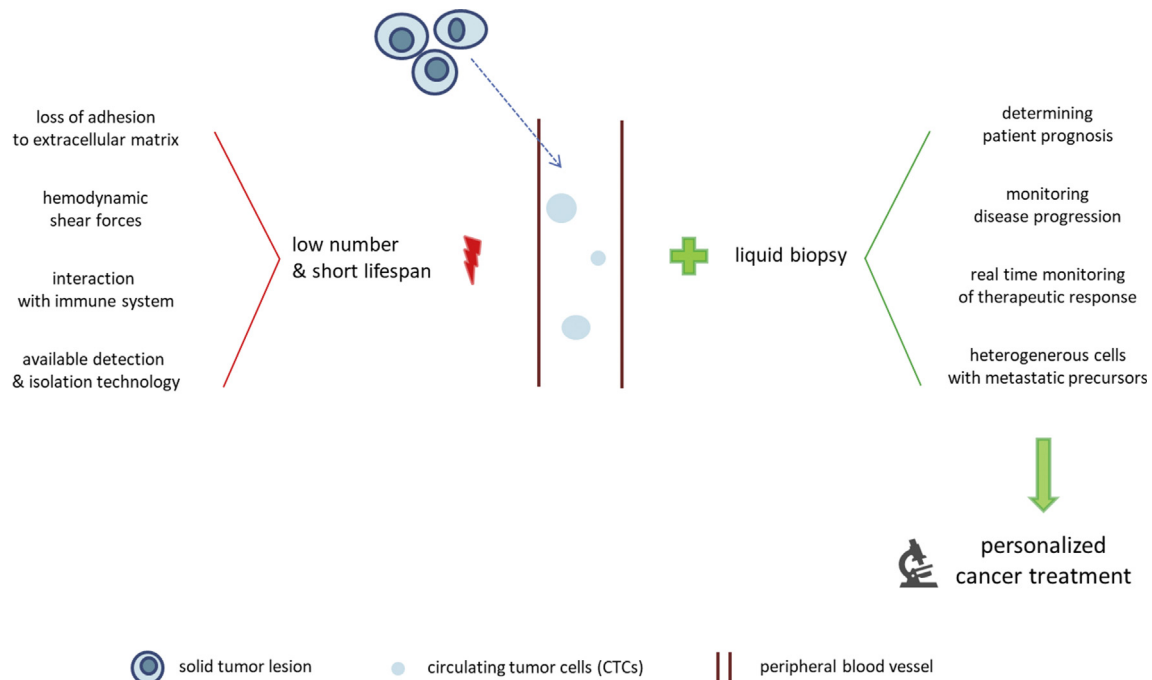


Fig. 1 Potential and challenges of using circulating tumor cells (CTCs) in cancer screening.

to non-small cell LC (NSCLC).<sup>5</sup> The most frequent subtypes of NSCLC include squamous cell carcinoma, large cell carcinoma and adenocarcinoma. NSCLC are less sensitive to chemotherapy and radiation therapy compared to SCLC.<sup>6</sup> Lung cancer screening in high risk groups as well as correctly diagnosing pulmonary nodules are hence essential strategies for avoiding the poor prognosis associated with asymptomatic and advanced lung cancer [1,2].

Ground glass opacifications (GGO) are a subset of pulmonary nodules that are or might become cancers. The tumor growth of cancerous GGO is slow and the risk of invasiveness is lower than in solid lung cancers.<sup>7</sup>

In an original article of this issue of *Biomedical Journal*, Wu et al. put forward a retrospective study in 500 patients with NSCLC, presenting with GGO lesions less than 2 cm. Since it is challenging to get pre-surgery tissue samples from small lesions, the goal of the study was to evaluate the treatment outcome between anatomic (sublobar) and wedge resection [1].

### Liquid biopsy in cancer

Screening and disease monitoring are also of major importance in the case of colorectal cancer (CRC) to decrease mortality in patients. Depending on the screening test applied, mortality can potentially be reduced through timely intervention between 18% and 57% [3]. The routine monitoring by serum carcinoembryonic antigen (CEA) assay however

<sup>5</sup> <https://www.medicalnewstoday.com/articles/316477>, last access 2022-01-03.

<sup>6</sup> <https://www.cancer.gov/types/lung/hp/non-small-cell-lung-treatment-pdq>, last access 2022-01-03.

<sup>7</sup> <https://pulmccm.org/review-articles/management-ground-glass-subsolid-pulmonary-nodules-review/>, last access 2022-01-03.

commonly provides false-positive results [4]. Another assay, the immunochemical fecal occult blood test (iFOBT), is affordable and non-invasive. It may identify CRC but also other issues such as polyps, ulcers or hemorrhoids.<sup>8</sup> The detection sensitivity of iFOBT though only lies at 60% [5].

In another article of this issue, Tsai et al. investigated subsets of circulating tumor cells (CTCs) in peripheral blood in order to find additional modalities to complement the above mentioned assays and improve disease detection [6].

CTCs, also referred to as “liquid biopsy”, are considered to be transforming the current landscape of cancer therapy due to their potential in many regards, including the determination of patient prognosis, monitoring tumor recurrence and therapeutic responses in real time [7]. CTCs are cells that departed from a solid tumor lesion and entered the bloodstream. Since they contain metastatic precursors, they provide insight into disease progression. Their heterogeneity reflects intratumor heterogeneity, potentially providing information not only for prognosis but also resistance to therapeutic approaches. CTCs are therefore highly promising as a basis for personalized cancer treatment [8]. Samples can be repeatedly collected with a high level of patient safety, and are less prone to errors than other, currently established cancer biomarkers [9].

The clinical application of CTCs however is still taxing due to the low number as well as short lifetime of CTCs in the blood, even further impacted by loss of adhesion to the extracellular matrix, hemodynamic shear forces, and interactions with the bodies' immune system. Additionally, currently available detection and isolation technologies prove to be insufficiently mature and need to be developed further [10] [Fig. 1].

<sup>8</sup> <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/immunochemical-fecal-occult-blood-test>, last access 2022-01-03.

Tsai et al. conclude that CTC testing delivers distinct results and could thus improve CRC screening by supplementing assays like CEA and iFOBT [6].

### **An independent animal**

In Ancient Greece, according to the Hippocratic gynecological writers the uterus was considered an independent animal, that would willfully move through the female body and cause disease, above all hysteria [11].

An agent that actually causes disease in the uterus is the Human papillomavirus (HPV). The virus comprises more than 200 subtypes and each of them is associated with a distinct set of clinical lesions [12]. More than 30 HPV types infect the genital tract [13] and at least 14 types are considered high risk since they are oncogenic.<sup>9</sup> HPV plays a major role in the development of cervical cancer (CC), although most infections are transient and can be spontaneously cleared by the immune system. In the case of persistent HPV infection, the progression to CC takes decades, hence clinical intervention allows for a positive prognosis if applied in time [14]. Even though early detection and timely treatment of precancerous lesions can prevent progression to CC, cellular abnormalities might be missed or insufficiently distinct [13]. Especially also in low and middle income countries access to preventative measures, like regular cervix screening and vaccinating girls and women against specific high risk HPV forms is limited. Beyond that, access to treatment of late stages like cancer surgery, radiotherapy and chemotherapy may be very limited in those countries. In 2018 CC was the fourth most common cancer death among women worldwide.<sup>9</sup>

In a further article of this issue, Sarabia et al. set out to evaluate the expression of repressor element 1-silencing transcription factor (REST) and the RAS association domain family member 1 A (RASSF1A) in cervical samples from 271 patients and CC derived cell lines. The team found altered expression of the gene expression regulator REST and tumor suppressor gene RASSF1A in squamous cell carcinoma (SCC) and squamous intraepithelial (SIL) lesions. Monitoring expression levels of REST and RASSF1A were hence proposed to be useful for SIL and SCC prognosis [15].

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## **Also in this issue**

### ***The trickiness of tuberculosis in transplant patients***

Tuberculosis (TB) is one the leading infections in recipients of solid organ transplant, as individuals with impaired immune response are more prone to develop TB from a latent or *de novo* infection than immunocompetent individuals. Since TB morbidity and mortality are high in post-transplant recipients, it is advised to perform risk-adapted screening as well as preventive chemotherapy to manage TB risk after transplantation [16]. However, according to the Taiwan CDC,

drug resistant TB is a consequence of improper use of antibiotics in chemotherapy of drug-susceptible TB patients. In multidrug-resistant tuberculosis the bacillus becomes resistant to the two most powerful anti-TB drugs, isoniazid and rifampicin (RFM).<sup>10</sup> Furthermore, TB treatment in transplant recipients is highly complex because of interactions between administered immunosuppressants and antibiotics [16]. Consequences might be an increase in the risk of graft rejection [17].

Since it is important to choose the right medication for effective treatment of TB, Wang et al. conducted a study to compare the safety, efficacy and clinical outcomes of RFM and rifabutin (RFB) in living donor liver-transplant recipients with active TB. Both drugs were confirmed equally safe and efficacious as part of an anti-TB treatment strategy. Additionally, Wang et al. found that RFB showed less drug interaction than RFM and proved to not significantly reduce the rate of acute cellular rejection [17].

### ***A biomarker for allograft dysfunction***

Chronic allograft dysfunction is a multifactorial process characterized by the progressive and irreversible loss of a transplanted kidney function. Contributing factors to the fibrotic changes in the graft are implantation stress, chronic immune system mediated rejection and infection. On that account, preventive measures and an individualized approach are essential to improve long-term outcome [18].

Aggan et al. present their work of elucidating the relation between the activity of the innate immune system and its relation to chronic allograft dysfunction in renal transplant recipients. They assessed macrophage activation reflected by serum soluble cluster of differentiation 163 (sCD163). The results suggest that the compound could serve as a potential biomarker for renal allograft dysfunction [19].

### ***Shock wave therapy in end-stage renal disease***

Managing coronary artery disease (CAD) currently relies on medication, percutaneous coronary intervention and coronary artery bypass grafting. However, prognosis is poor in cases where those therapeutic options are not applicable. In 2006, extracorporeal cardiac shock wave therapy (ESWT) on human has been reported for the first time. It proves to be effective and safe in reducing myocardial ischemia [20,21]. Sung et al. were curious to find out if ESWT would alleviate symptoms in patients with end-stage diffuse CAD (EnD-CAD) and simultaneous end-stage renal disease (ESRD). The researchers performed a small-scale prospective study and saw beneficial effects of ESWT in EnD-CAD patients. On the contrary, long-term effects on angiogenesis and left ventricular ejection fraction were reduced for EnD-CAD patients with concomitant ESRD. Sung et al. therefore recommend to carefully evaluate the application of ESWT as therapeutic modality in the case of ESRD/EnD-CAD [22].

<sup>9</sup> [https://www.who.int/en/news-room/fact-sheets/detail/human-papillomavirus-\(hpv\)-and-cervical-cancer](https://www.who.int/en/news-room/fact-sheets/detail/human-papillomavirus-(hpv)-and-cervical-cancer), last access 2022-01-06.

<sup>10</sup> [https://www.cdc.gov.tw/En/Category/ListContent/bg0g\\_VU\\_Ysrqkes\\_KRUDgQ?uaid=0WialNbsh7SEGERJLa29FA](https://www.cdc.gov.tw/En/Category/ListContent/bg0g_VU_Ysrqkes_KRUDgQ?uaid=0WialNbsh7SEGERJLa29FA), last access 2022-01-05.

### Saving transplanted $\beta$ -cells

Type 1 diabetes mellitus (T1DM) is a multifactorial autoimmune disease characterized by immune-mediated destruction of pancreatic  $\beta$  cells in the islets of Langerhans. Tight glucose monitoring and frequent exogenous insulin therapy is required to maintain normoglycemia.  $\beta$ -cell replacement therapy via islet transplantation constitutes an alternative therapy approach, although inflammatory reactions reduce islet survival. Encapsulating islets in an immunoprotective envelope may shield the transplant from direct immune cell-to-cell contact [23] and most protocols include inhibitors to maintain immunosuppression in alloislet recipients [24]. Murine models demonstrated that islets transplanted in the renal sub-capsular space are not exposed to non-specific immune responses, in opposition to intra-liver islet engraftment, which is the standard clinical practice performed in humans [25].

Often two or more clinical islets transplantations in humans are needed to increase the success rate. Some incretin hormones improve  $\beta$ -cell survival, however, they are rapidly degraded by dipeptidyl peptidase (DPP)-IV. To explore this relationship further, Juang et al. treated 150 diabetic mice with a synthetic DPP-IV inhibitor after syngeneic, subrenal capsule transplantation. The research team confirmed their hypothesis that the effect of the inhibitor depends on a critical mass of implanted islets. Otherwise it does not exert a significantly positive effect on  $\beta$ -cell survival and proliferation [26].

### Susceptibility to cancer in arseniasis areas

The toxic metalloid arsenic naturally occurs in inorganic forms in surface and groundwater reservoirs where it can be easily solubilized depending on factors like pH, redox conditions, temperature, and solution composition. Man-made sources, such as mineral extraction, processing wastes, livestock feed additives and pesticides, contribute to arsenic contamination of food and drinking water [27]. Studies suggest that there is a dose–response relationship between chronic, accumulative arsenic exposure and diseases such as diabetes mellitus [27,28] and risk of cancer [29–31]. However, the cancer occurrence seems to be additionally related to the genomic susceptibility and individual metabolism of inorganic arsenic. In order to find potential preventive strategies for arsenic carcinogenesis, Liao et al. performed a follow up study in 96 individuals from an arseniasis area in Taiwan, where the study subjects had been exposed to arsenic contaminated water in the early 1990s. Liao et al. found that a high inorganic arsenic methylation response at the primary stage may foster the onset of various cancers in a dose-dependent manner. They further determined genomic markers in residents of arseniasis-endemic regions that hint at a higher risk of developing various cancers [32].

### Bladder volume

The origins of musical instruments extend back to prehistoric times. A few instruments that survived as well as cave paintings allude to a broad variety of musical tools. Wind instruments for example are found in different forms across the globe. They were probably discovered independently by

early cultures through vibrating the lips against a hole in a branch, a bone, a shell, an animal horn or tusk.<sup>11</sup>

Between the 14th and 16th century the bladder bagpipe was a popular instrument across Europe, although after losing in fame, it would be later on associated with beggars and peasants.<sup>12</sup> The specific properties of an animal bladder as wind reservoir enabled the player to articulate by using a continuous air flow in addition to easily stopping and starting. In contrast to a bagpipe, where arm pressure is exerted on animal skin, an animal bladder offered the advantage of expelling air down the pipe on its own through elasticity.<sup>13</sup>

Maintaining bladder volume is also essential in a different context, the treatment of prostate cancer. Radiotherapy for prostate cancer achieves high local tumor control, and maintaining bladder volume during radiation treatment minimizes its toxicity. However, especially elderly patients may have difficulties with retaining a full bladder during procedure. Protocols to enhance bladder volume reproducibility involve the consumption of water although recommended amount vary. Chen et al. reviewed 11 studies and determined 300–400 ml of water to be the optimal quantity for maintaining the best bladder volume reproducibility [33].

### Detecting various stages of diabetic retinopathy

Service dogs play an essential role in the lives of individuals with disabilities. The animals are trained to mitigate the effects of physical, sensory, psychiatric, intellectual or mental disabilities of their owners.<sup>14</sup> In the case of diabetes, there are two types of service dogs: the medical response dog that reacts to symptoms of severe low blood sugar and retrieves items such as food, drinks or an emergency kit for their owners. The diabetic alert dog on the other hand alerts the concerned individual of dangerously low or high blood sugar before that person becomes symptomatic. Mark Ruefenacht, founder of dogs for diabetics, D4D, trained the first diabetes service dog in the world. He got involved with service dogs due to his family history of diabetic retinopathy (DR).<sup>15,16</sup>

DR is one of the most present ophthalmic diseases next to glaucoma, cataract and age-related macular degeneration worldwide [34]. DR occurs in approximately one third of people with diabetes and onset and progression are triggered by various factors including poor control of blood glucose and elevated blood pressure. The following change in vascular permeability of the blood-retinal barrier occurs and *inter alia* entails capillary occlusion, retinal ischemia, macular edema and leakage of fluid and blood into the retina [35]. Symptoms

<sup>11</sup> <https://www.britannica.com/art/wind-instrument/The-history-of-Western-wind-instruments>, last access 2022-01-02.

<sup>12</sup> <https://www.music.iastate.edu/antiqua/instrument/bladderpipe>, last access 2022-01-02.

<sup>13</sup> <https://www.encyclopedia.com/arts/dictionaries-thesauruses-pictures-and-press-releases/bladder-pipe>, last access 2022-01-02.

<sup>14</sup> <https://udservices.org/blog/types-of-service-dogs/>, last access 2022-01-04.

<sup>15</sup> <https://diatribe.org/diabetes-ruff-diving-world-diabetes-service-dogs>, last access 2022-01-04.

<sup>16</sup> <https://ourdogssavelives.org/programs/d4d/>, last access 2022-01-04.



usually only present in an advanced stage of DR. Accordingly, screening of risk patients within regular intervals is highly recommended [34].

In the search for biomarkers as diagnostic tools, Helal et al. performed a study in 80 type 2 diabetic patients with severe DR. The research team looked at the serum expression of miRNAs and found two miRNAs that were increased and one that was decreased with the severity of DR. They consider all three miRNAs as promising candidates for detecting mild, moderate and severe stages of DR [36].

### **Fungi as freeloaders in leukemia patients**

Age is a major risk factor for many human cancer forms, including leukemia. Studies concluded that cancer incidences climb dramatically with age, peaking at 80 to 85. Considering the growing number of elderly in populations worldwide, concerns are voiced about the impact this has on public health systems, in particular in the face of rising cancer incidences [37].

Individuals with acute myeloid leukemia (AML) have a heightened risk of fungal infections. This is due to periods of neutropenia caused by chemotherapeutic agents. The degree and duration of neutropenia correlate with the risk of invasive fungal infections (IFIs). IFIs are a major cause of mortality and morbidity in AML patients [38].

The research team Chang et al. explored the incidence, clinical features and outcome of hepatosplenic candidiasis (HSC), a rare type of IFI, in AML patients. Their retrospective review of charts in a Taiwanese hospital revealed that patients were most susceptible to HSC during the first phase of chemotherapy, induction or re-induction. Prolonged neutropenia constitutes a poor prognosis factor for HSC and Chang et al. advise early screening and prompt antifungal treatment in risk patients [39].

### **Inhibiting the effect of rat lungworm secretions**

The neurotropic parasite *Angiostrongylus cantonensis* is the most common cause of eosinophilic meningitis and eosinophilic meningoencephalitis. The nematode is mostly present in Southern Asia, the Pacific and Caribbean islands and spreads through infected rats on ships. The main route of infection in Thailand for example is through ingestion of raw or undercooked snails. The physical destruction of neural tissue found in patients can be partially explained by larvae migration [40]. However, helminths are also known for producing excretory-secretory products (ESPs) to modulate host immune responses [41,42].

Since 3-Hydroxybenzaldehyde (3-HBA) and 4-Hydroxybenzaldehyde (4-HBA) represent potential drugs in response to *A. cantonensis* infection, Chen et al. examined the drugs' effects on cells treated with ESPs from the parasite. They demonstrated that cell viability of astrocytes was successfully increased since 3-HBA and 4-HBA inhibit apoptosis-related molecule expression [43].

### **Re-inventing acupuncture needles**

Acupuncture as part of Traditional Chinese Medicine is thought to be several thousand years old, although originally

sharpened stones and bones were used around 6000 BCE instead of needles made from metal.<sup>17</sup> Intriguingly, the 5000-year-old mummified body of Ötzi, the Iceman, presents 15 groups of tattoos on points that coincide with acupuncture points for abdominal and lower back issues. The material used for acupuncture treatments changed later on, around 800 BC bronze needles were utilized, and around 200 BC gold needles were made. Nowadays acupuncture needles are usually made of stainless steel shafts with handles of copper or steel [44].

In the search for new needle materials, Wang et al. set out to explore the needling sensations of acupuncture needles treated with nitrogen applied supercritical fluid (SCF-N). They compared the effect to the effect produced with conventional stainless steel needles. The double-blind cohort study revealed that SCF-N treated needles enhance sensations and improve electrical conductivity of meridians [45].

### **Antibiotic resistance in *Helicobacter pylori* treatment**

An infection with *H. pylori* affects approximately 50% of adults. The bacteria are associated with a wide range of upper gastrointestinal diseases like gastritis, peptic ulcers and gastric cancers. The efficacy of the standard triple therapy with a proton pump inhibitor (PPI) and two antibiotics is inversely related to bacterial load. However, resistance to antibiotics and treatment duration led to the development of another first-line approach, containing a different PPI and additionally a nitroimidazole. The concomitant or non-bismuth containing quadruple therapy reduces the complexity of the sequential triple approach. It also offers higher eradication rates even in patients with resistance to clarithromycin [46].

Huang et al. analyzed the efficacy of concomitant therapy in 246 patients in a Taiwanese hospital during a period of increasing clarithromycin resistance in Taiwan. The success rate of the treatment decreased with changes in antibiotic resistance [47].

### **Two approaches in a challenging malocclusion case**

Skeletal Class III malocclusion is established early in life and is characterized by protrusion of the lower jaw. Nonsurgical treatment of the dentofacial deformity proves to be challenging and the timing of treatment is crucial for a successful outcome especially in young patients [48].

Insawak et al. focused on comparing 3D dental movement in two different approaches of phase orthognathic surgery in 40 patients with class III malocclusion. The occlusion outcome was determined to be the same in both, the orthodontic-first (OF) and surgery-first approach (SFA) [49].

### **A non-coding RNA in breast cancer...**

Long non-coding RNAs (lncRNAs) often function as master regulators for gene expression as they are able to interact with DNA, RNA, or protein. Consequently, they may play a critical

<sup>17</sup> <https://www.news-medical.net/health/Acupuncture-History.aspx>, last access 2022-01-06.

role in various biological processes including diseases like cancer [50].

The lncRNA MALAT1 is aberrantly expressed in tumor tissues and/or body fluids and may hence serve as biomarker for tumor diagnosis and prognosis [51].

Yue et al. assessed *in vitro* the role of MALAT1 in breast cancer (BC) progression with the focus on elucidating its role in doxorubicin resistance. Doxorubicin is a first-line chemotherapeutic drug in treating BC. Yue et al. found MALAT1 to be upregulated in BC cells. Additionally, it targets the miRNA-570-3p and is suggested to thus contribute to doxorubicin resistance [52].

### ... and in lung carcinoma

Another oncogenic lncRNA is HAGLROS. In lung carcinoma its expression is correlated with tumor stage, proliferation and migration of cancer cells because of the molecule targeting specific microRNAs [53].

Li et al. investigated *in vitro* the expression characteristics, function and mechanism of HAGLROS expression in NSCLC. The lncRNA expression is upregulated in NSCLC and over-expression promoted malignant phenotypes of NSCLC cells. Furthermore, HAGLROS potentially targets miR-100, which is involved in apoptosis and autophagy. Additionally, HAGLROS expression is negatively correlated with SMARCA5 expression, a crucial regulator in gene transcription, DNA repair and DNA replication [54].

### Conflicts of interest

The author declares no conflicts of interest.

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