Oncology news

Volume 13 Issue 2 • March/April 2018 • www.oncologynews.biz

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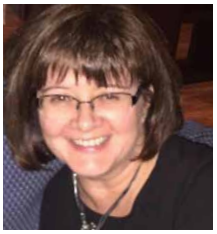
Oncology News under new management

When BioMedES UK (www.biomedes.biz) took over in September 2017, it had to bring in new management to cover the tasks it presents. We are pleased to say that in all there will be five people on the team. Our Marketing and Publishing Manager is Shona Owen, who has an extensive local government and 3rd sector background; she also helps manage the Aberdeen Chamber Orchestra. The Design and Web Manager is Claire Hamilton, who is experienced in the printing and publishing world. You will see considerable changes in our website as it undergoes reconstruction. A regular member of the team is Angela Panther, who has been a personal assistant to the editor for almost 20 years (editor@oncologynews.biz). Two other team members will shortly be joining us, a finance officer and a copy editor (they will be introduced in the next issue).



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Meet the Editorial Team

Professor Denys Wheatley is Editor, and is Director of BioMedES. He hasstrong research ties in Albany, Davis, Auckland, Valencia, Detroit, Budapest, St Petersburg, Heidelberg, Zürich and Hong Kong. He is eager to establish strong interaction with cancer and cell biology teams worldwide, and initiate programmes in the areas in which his expertise lies. His work in cancer research, other scientific fields, with IFCB, and in publishing and scientific communication has led to his receiving awards in recent years.

Dr Richard J Ablin (Associate Editor), is Professor, Pathology, University of Arizona College of Medicine and a Member of the Arizona Cancer Center, Tucson, Arizona. He received the First Award for scientific excellence from The Haakon Ragde Foundation for Advanced Cancer Studies. Dr Ablin discovered prostate-specific antigen (PSA) in 1970. A pioneer of cryosurgery and cryoimmunotherapy, he has extensive experience in cancer research.

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Farrokh completed his higher surgical training in London, during which he was selected onto the highly competitive National Oncoplastic Fellowship program.

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Dr Brandon Reines, is Adjunct Assistant Professor at the Department of Biomedical Informatics, University of Pittsburgh School of Medicine. He is an expert in human and veterinary cancers, with a particular interest in the underlying hypotheses on which advances can be made in cancer research.

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Volume 13 Number 2 • March/April 2018

Oncology News has a wide distribution, reaching thousands of people, especially being online with free access. Under new management, its readership will rise by going increasingly global. It is now extending its range of articles by including professionals concerned with other aspects of cancer than those involving oncologists and cancer researchers, from campaigning to counselling, from diet to massage. Cancer is a very complex disorder that ultimately requires personalised medicine that can only be delivered by integrated teams of doctors. In an age when even GPs move into their own specialist areas, they need to follow advances in our understanding of cancer across the whole spectrum by updating themselves through a journal like Oncology News.

We also cover conference notices and reports, review journal papers and books, publish an events diary, release news from cancer from Institutions and companies, promote cancer charities, and advertise commercial products. Articles cover a multitude of facets, e.g. from how to massage cancer patients to the replacement of a cancerous oesophagus by using the lower bowel. They are written in a style that the interested layman should also be able to understand.

Oncology News is published by BioMedES Ltd.
Leggat House, Keithhall, Inverurie, Aberdeen AB51 0LX, UK.
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The N.N. Alexandrov National Cancer Centre, Belarus

Cancers – getting to grips with the "rare" ones

Denys Wheatley
Editor

I have repeatedly endorsed the view that all cancers are unique. In the last decade or so this has been borne out by the fact that it is never clear how any tumour might behave before or after treatment, so that vulnerable patients now have teams of experts following developments. Having a relatively predictable outcome in many types of tumour helps in deciding the appropriate treatment, otherwise regularly used protocols would be a thing of the past. However, some tumours of particular tissues are indeed "rare", and while this can occur at any age, they more frequently develop in the young rather the old. In childhood there is a preponderance of tumours of the nervous system for some reason, such as ganglioglioma and medulloblastoma. These tumours can arise in one in 100,000 infants or even fewer. It was therefore a surprise to have an indication from Cancer World that 20% of cancers are considered rare; that's I in 5! The issue becomes one of what constitutes rarity, a problem topping the list of the new rare cancer network project backed by the European Commission. There are figures available elsewhere, but hugely less than 1 in 5. Some typical figures worldwide are 1 in 1,500 in the USA, 1 in 2,000 in Europe, and 1 in 2,500 in Japan. Hence there is a figure already there for Europe, but the literature also indicates that the incidence of rare cancers ranges massively from 1 in 1,000-2,000 to as few as 1 in 200,000. Some GPs will probably have never encountered one of the rarer tumours in a whole career, and some specialists might have dealt with no more than a small handful. The literature is an obvious source of information on how to diagnose and treat rare cancers, but pulling together this scattered information, especially from the past - often when CT or gene sequencing had still to be discovered - is not going to be particularly useful today.

It is quite clear that databases need to be formed for considerable geographical areas, with appropriate epidemiological information. Having decided what the criterion is of "rare", a list can be drawn together by those encountering such cases, reporting them to the European Network Project called RareCare (www.rarecare.eu). In its own promotional literature it has already indicated that a figure of 1 case in about 15,000-20,000 is expected, but this has been based on cancer registries compiled 15-20 years ago, i.e. considerably lower than given above by an order of magnitude. Clearly updating is very important, for surely new methods of diagnosis, particularly gene sequencing, must have seen the incidence rate rise considerably over the last 1-2 decades.

To date over 22 European countries have signed up, but it all depends on oncologists providing relevant and accurate data. A team of true experts is in place to sift through the submissions - no small task, but it should yield interesting results. The information will tell us what the full burden of rare cancer might be, and provide more up-to-date information on individual cases. This will help diagnosis and treatment, and oncologists - not just those in Europe, but in the rest of the world - should benefit by diffusion of the information through global networks. Data analysis might reveal some unexpected trends, procedures that lead more precise diagnosis, and hopefully specific protocols that are more suitable for the treatment of the most unusual tumours.

The data hopefully will also help in classifying more accurately the types of tumours considered rare, which should improve the International Classification of Diseases in Oncology. These steps move in the right direction by bringing together the forces that can do something about the tricky business of managing and treating rare tumours. Implications regarding the cost involved might emerge. Modern equipment is need that can approach these tumours from a new perspective, such as proton therapy, successfully used on childhood neural tumours, for example in St. Petersburg at the Centre of Nuclear Medicine in the Sergey Berezin Medical Institute. But to return to one of my initial points, tumours all differ from one another, some only slightly, but others quite radically. So the question becomes: do these rare tumours, let us say gangliogliomas, have much on common or is each one quite different from another? It would be heartening to believe that it is the former, i.e. that they have arisen in a similar manner in each case through some common defect in a developmental process. Only time will tell, but the "comparing of notes" within the continent and between them should soon bring up some useful information, and oncologists will not be working so much in the dark on rare cases.

The N.N. Alexandrov National Cancer Centre, Belarus

223040 Lesnoy, Minsk District, Belarus

The N.N. Alexandrov National Cancer Centre of Belarus is a Unified Scientific, Medical and Diagnostic Complex and the leading cancer centre in the country (Figs. 1 and 2). It includes 9 research departments, 28 diagnostic and treatment subdivisions, including a molecular genetic laboratory, a positron emission tomography center and a gamma knife. The center was founded more than 55 years ago. More than 19,000 patients throughout Belarus and from other countries undergo medical examination and treatment every year.

Figure 1: *N.N. Alexandrov National Cancer Centre*

Figure 2: *Molecular Genetic Laboratory*

The centre is headed by Professor O.G. Sukonko, who is a leading specialist in the field of urological oncology in the Republic of Belarus. The specialists at the centre apply the most effective methods of surgical, radiotherapeutic, chemotherapeutic, combined and complex treatments of all types and localizations of malignant tumors practiced in medicine worldwide. In 30 well-equipped operating theatres complex and high technology operations are performed for tumours of the head and neck, breast, lung, esophagus, stomach, colon and rectum, urogenital organs, bones and soft tissues.

Four modern linear accelerators make it possible to implement the intensity modulated radiotherapy (IMRT), stereotactic, 3- and 4-D conformal radiation therapy. A gamma–therapy machine and 2 brachytherapy suites are also available. When and where necessary, treatments are supplemented by radiofrequency ablation of tumors and interaction with other agencies (e.g. hyperthermia, photodynamic therapy). Intraoperative intraperitoneal or intra-pleural thermo-chemotherapy is used for patients with disseminated malignant lesions of the pleura and peritoneum. In 2009, Assembly, the Centre was awarded the "European Quality" award by the Nomination Committee of European Business (Fig. 3).

Figure 3:

Research in etiology and pathogenesis of malignant tumors in adults is conducted by the Centre to work out methods for prevention, diagnosis and treatment (surgical, radiation, medicinal, combined and complex) of malignant tumors. Prophylactic medical examination and rehabilitation of cancer patients are also carried out. In 2017, the Center received the Certificate of Accreditation issued by the European Training Centre in Gynecological Oncology, ESGO

The National Cancer Centre in Belarus is a high-ranking medical establishment having top-notch up-to-date equipment, utilizing advanced technologies, providing leading-edge integrated all-round approach to treatment. In this regard, its forward thinking approach means that it has hope to further develop:

1. Photolon-mediated photodynamic therapy
2. Hyperthermic intraperitoneal chemotherapy (HIPEC) for radical operation of gastric cancer patients
3. General hyperthermia with artificial hyperglycemia
4. Tissue engineering in tracheal transplantation

More information is available on the Center's website: www.eng.omr.by

[N.B. Oncology news will in future be running feature articles on leading cancer centres around the world, of which there are very many. If you would like your institute to be included in future issues, please get in touch with the editor (editor@oncologynews.biz), especially those that have recently come on the scene. Our first feature is on the main cancer centre in Belarus, kindly provided by Dr. Mihail_ Revtovich (mihail_revtovich@yahoo.com)]

Lung Cancer Screening

Mark S. Parker, Robert C. Groves, Joanna E. Kusmirek, Leila Rezai Gharai and Samira Shojaee. Published by: Thieme Publishers, ISBN:9781626235137

The book written by Mark Parker and colleagues presents a succinct introduction to lung cancer screening, especially from the point of view of the development of a lung cancer screening programme. This view of the screening programme give special emphasis on reporting of cancer screening reports, eligibility of patients and unexpected findings such as osteoporosis or thyroid lesions.

The case for screening programmes for lung cancer is well presented, through the first three chapters on Lung Cancer Epidemiology, Risk Factors for Lung Cancer and Evolution of Cancer Screening. It is striking that Lung is the only of the four deadliest cancers (prostate, breast and colorectal being the other three) that is not subject to routine screening.

The book presents a well-balanced discussion of pros-and-cons of screening, probably the main disadvantage is the radiation exposure that is required for screening with Computed Tomography. However, the opportunity of early detection of cancer when resection is possible, especially for populations at risk, i.e. smokers, outweighs the hazards of the exposure that is maintained at the "ALARA" (as low as reasonably achievable) level.

The chapters on the presentations of lung cancer are probably a bit too short and could benefit with more detail for readers who are not totally comfortable with the diagnosis of lung CTs. Some details, like arrows pointing nodules, lymph nodes, apical posterior segments, would be useful, as well as clarification of terms that may not be familiar like "lepidic growth patterns".

The chapter on the future of cancer screening is particularly interesting, especially the use of novel biomarkers such as microRNAs, circulating autoantibodies, salivary microbiota and exhaled biomarkers. It may be that in a few years' time Computed Tomography will be displaced as the technology of choice for lung screening.

Overall it is an interesting book, and one that will be on the shelf of the Lung Screening offices around the world.

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Tickling the Giant - a physicist's (Mike Retsky's) mathematical view of how cancer grows can suggest new ways of treating cancer with existing drugs

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Mike Retsky

If you were a novelist looking for a prototype for a modern-day David, you could do no better than Michael Retsky. At 78, he has an impish smile, and a personable low-key way of talking. That, and an astute mathematical mind, may be why he has fared as well as he has against his chosen Goliath - cancer. With colleagues, he has proposed counterintuitive therapies to prevent relapse in colon, breast and other cancers. But Retsky's vantage point is not that of a complete outsider, at least not professionally. As a Harvard Research Associate in the prestigious Folkman lab, Retsky has tried to make change from the inside - by taking aim at Goliath's head, or more precisely, his "brain." Analyzing ingrained thinking patterns and resistance to any truly new ideas - except those that produce a new patentable chemical entity - led Michael to doubt the validity of much current oncology practice. Perhaps the main reason for his unusual capacity to step back and take an objective view of a whole field of biomedical research is his educational background. Originally trained in experimental physics, Retsky did not exactly choose to go into cancer research. He was more or less pulled in by brushes with the disease itself, first a friend and then himself, leading to a courageous, but little-known self-experiment, and a new treatment approach.

Nonetheless, instead of just accepting current treatment approaches as sacrosanct, he delved deeply into the original data upon which standard practice is based. His resulting critique runs the gamut from exposing faulty reasoning underlying maximum tolerated dose (MTD) chemotherapy to suspecting an iatrogenic cause for most early breast cancer recurrences. His research started in the early 1980s, while developing electron-beam technology at Hewlett Packard, and when lymphoma was diagnosed in a co-worker's wife. To help out, Michael conferred with oncologist, Jack Speer, who explained the rationale behind MTD chemotherapy. Retsky's first surprise was realizing how few studies justified such draconian treatment, and that one of the main ones was completely erroneous. Anna Laird's experiments at one of the US atomic weapons labs ostensibly showed that solid tumor growth is just short of exponential or Gompertzian1. It is that rapid growth tailing off that has been used to justify "pushing to toxicity" by MTD chemotherapy for 6 months,2-4 which can lead to dreadful side effects.

However, Retsky recalls, "there is a basic mathematical flaw that is repeated 19 times in the Laird papers. And it was just a small animal experiment, involving 18 rodents and a rabbit." This led him to look for large human databases that might allow him to determine tumor growth rates directly in actual patients. Breast cancer data were abundant and of high quality. Between 1982 and 1990, Retsky acquired large data-sets that showed tumor sizes at different time-points, analyzed them, and created computer simulations allowing him to test various models, including Gompertzian kinetics. Once analyzed by computer simulation, the data clearly refuted that model, and suggested instead that solid cancers grow rapidly only intermittently, with long periods of fractions of years or whole years of complete dormancy5-8. In that light, Michael recalls wondering in 1993 - does it make sense to blast a recently diagnosed patient with high dose chemotherapy for 6 months, when the tumor may not have a growth spurt until a year out? Is there an alternative to short-term maximum tolerated doses that may do a better job of killing tumor cells and possibly eradicating (curing) cancer in some patients?

As fate would have it, an unexpected opportunity - and motivation - for developing a new treatment and to begin testing it presented itself in 1994, when Retsky was diagnosed with stage IIIc colon cancer. The cancer had spread to four lymph nodes, but not could tell to any distant organ as far as his doctors. "I wasn't as anxious as most people are about it, because I had been studying cancer for over a decade, and was hopeful that my ideas would work better than standard treatment to prevent further spread and recurrence," he recalls. Having discovered that breast cancer grows in fits and starts, with dormancy periods as long as a year, and that the usual high-dose chemotherapy damages every body system and makes the patient miserable, Retsky specifically designed a treatment for his cancer that would instead be long-term and low-dose. The chemotherapy would be given daily for two and a half years at 30% less than the usual dosage. Prior work with "infusional chemotherapy" had shown that a dose of 300mg/m2/day was associated with minimal

toxicity9. Retsky's goal was a long-term treatment with no toxicity, so he opted to use 200mg/m2/day 5 FU.

Since the treatment would continue for so long, he worked out a system that would make each treatment part of his daily ritual. In order to be workable, he felt it should involve minimal disruption to his normal lifestyle and work routine. His oncologist placed infusion tubing in his upper chest. Retsky ran his own infusion for 5 hours every night with a small portable pump, which he says was quiet enough, so that he and his wife could sleep comfortably. In 1996, after the first 2 years of treatment, Retsky was hired as a research associate by Judah Folkman at Harvard Medical School10. He felt confident enough in his treatment approach, since he was doing fine and had experienced only numbness in his fingers as a side effect, to ask Folkman if someone in the lab would investigate whether chronic low-dose chemotherapy might inhibit vascularization (neoangiogenesis) of growing tumors, for which Folkman was already well known. Folkman brought along researcher Tim Browder, who eventually tested 5-FU delivered in low doses for protracted periods, and found that indeed such "metronomic chemotherapy" is anti-angiogenic.

Remarkably, although published in Cancer Research in a paper that has been cited 1100 times,11 and tailored to the documented natural history of human solid cancers (instead of an erroneous rodent experiment), metronomic chemotherapy has been used mainly either after high-dose chemotherapy for early stage disease or for frail patients in advanced stages12,13. But, as a genuine alternative to standard 6 month MTD adjuvant therapy for early stage solid tumors which have spread to nodes, metronomic chemotherapy has yet to be tested in a controlled human trial. What stands in the way? "The current system is heavily biased towards development of new drugs, rather than better use of existing drugs," Retsky insists. "This also means that what is considered valuable research tends to be of an esoteric molecular kind, and not the kind I do, which looks at whole cancers, and where and when they grow in the bodies of real patients. And from a corporate standpoint, doing controlled human trials is extremely expensive, and drug companies are reluctant to spend millions if there is no potential profit from it. An individual investigator like me has to come up with a significant cost of the trial, according to current National Cancer Institute rules. "

Although trying to educate patient advocacy groups about such matters, in late 1996, while still hooked up to an infusion pump every night, Retsky returned to his original interest, breast cancer. This disease continues to kill approximately 40,000 American women every year, as it had for half a century, and mammography and adjuvant chemotherapy were not producing the expected benefits.14,15 What could explain the minimal progress? Retsky recalls wondering at the time, were the accepted models of breast cancer recurrence either slightly or completely wrong, as he had found for chemotherapy dosing? He traces his first new insights about breast cancer recurrence to a chance meeting at a cancer conference in 1993, with another physicist turned cancer researcher. Romano Demicheli was presenting data from 1,073 women with breast cancer treated by mastectomy at the Milan National Cancer Institute, and followed for 15 years16. "What jumped out at me from the graph he showed was two distinct recurrence peaks, the first and most dramatic one within a few years of surgery, and the second 5 to 6 years after it. The first peak was so high and narrow; I felt there had to be some earlier event synchronizing metastatic growth in these women from 9 to 18 months out, when the cases were most tightly grouped."

But what might trigger growth of micro-metastases in the liver or other organs in so many women all at the same time so soon after surgery? Retsky and Demicheli's further detective work led them to a shared and very daunting conclusion: it had to be the self-same surgical removal of the primary tumor that was accelerating metastatic growth17-21. "We knew that from a politics of research standpoint, this was the worst possible result,"Retsky recalls, "but as two trained physicists, we were excited that we could explain a variety of quantitative anomalies, not just the recurrence pattern." Another thorny breast-cancer anomaly is that, in controlled trials, women under the age of 50 who undergo mammography have a slightly higher mortality from breast cancer than those who are not screened. This was first shown in Canadian studies in the 1990s,22 when a some epidemiologists suggested the diagnostic X-ray could have worsened outcome,23 but this was never borne out.

Instead, Retsky and Demicheli argued that mammography was detecting smaller and smaller tumors, a few of which may have already seeded small growths in distant organs - and growth of those micro-metastases is enhanced by surgical removal of the breast tumor in about 20% of young women with lymph nodes positive for cancer24. At no point, however, did Retsky and Demicheli advocate leaving the primary tumors in place. The question was what additional intervention at or around the time of surgery might prevent the acceleration phenomenon.

It was not until 2010 that a clue finally arose, again from an anomaly in human trial results. The Belgian anesthesiologist, Patrice Forget, published data from 327 patients showing, remarkably, that a pain-killing drug given at the time of surgery seemed to affect overall survival. In particular, the patients receiving the non-steroidal anti-inflammatory drug (NSAID), ketorolac, prior to surgery and conventional adjuvant therapy had far fewer recurrences than those

taking another pain killer25-27. The expected first and worst peak of recurrences from 9-18 months was all but eliminated (Figures 1 and 2).

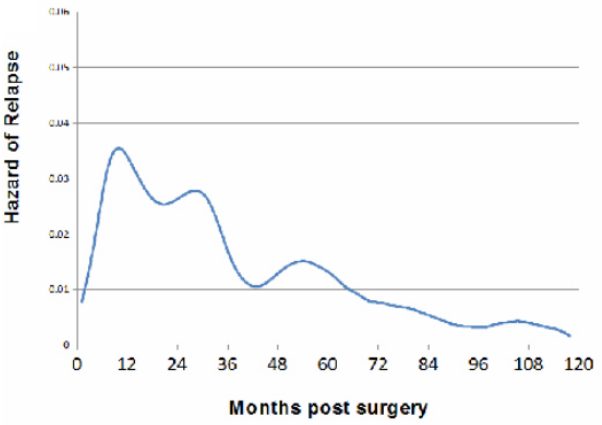

Figure 1: *First recurrence clusters of breast cancer in a remote organ occur in a biomodal pattern from 9-18 months to 3 years*

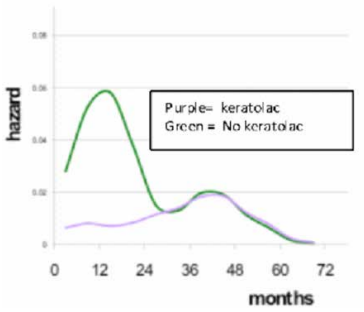

Figure 2: *The NSAID ketatolac virtually eliminated first cluster of metastatic breast cancer recurrences following surgery*

Once again, as in the case of metronomic chemotherapy, Retsky found himself up against Goliath's brain - a government-industrial-academic complex that perceives his discoveries as not only unprofitable, but decidedly low-brow. It is true that academic accolades and Nobel prizes are unlikely to flow from setting up controlled human trials of various NSAIDs given at the time of cancer surgery. Based on current data, however, just such experiments are the best bet for curing more patients of breast cancer. Undaunted, in fact, over the past 6 years Retsky has spent countless hours in Nigeria and India, meeting with oncologists at the larger hospitals, hammering out agreements for setting up controlled trials of ketoralac for triple negative breast cancer - once he is able to secure funding. "If we could get just a fraction of the hundreds of millions spent on cancer genetics allotted for trials of perioperative NSAIDs, we could cut the death rate from breast cancer by as much as 50%. Real precision in treating individual patients won't come from just knowing their genes, but understanding where and when their cancer is growing in their body, and finding highly targeted ways of preventing acceleration of metastatic activity that occurs in the week post-surgery."

It is ironic that, in an age of evidence-based medicine, our most prestigious treatment strategies are either non-theoretical, based on gene associations ("precision" medicine), or on theories that are easily refuted by existing data, such as maximum tolerated dose chemotherapy6. Given Retsky's work, perhaps it is time for a new rubric in the medical lexicon- evidence-based theory. This would take biomedical science a step closer to a realistic model of how physical sciences really advance, and provide a better sling for cancer theorists to wield.

References

1 Laird, A. K. Dynamics of growth in tumors and in normal organisms. Natl Cancer Inst Monogr 30, 15-28 (1969).
2 Skipper, H. E. Kinetics of mammary tumor cell growth and implications for therapy. Cancer 28, 1479-1499 (1971).
3 Norton, L. A Gompertzian model of human breast cancer growth. Cancer Res 48, 7067-7071 (1988).
4 Retsky, M., Swartzendruber, D., Wardwell, R., Bame, P. &Petrosky, V. Re: Larry Norton, a Gompertzian model of human breast cancer growth. Cancer Res 49, 6443-6444 (1989).
5 Retsky, M. W., Wardwell, R. H., Swartzendruber, D. E. & Headley, D. L. Prospective computerized simulation of breast cancer: comparison of computer predictions with nine sets of biological and clinical data. Cancer Res 47, 4982-4987 (1987).
6 Retsky, M. W., Swartzendruber, D. E., Wardwell, R. H. &Bame, P. D. Is Gompertzian or exponential kinetics a valid description of individual human cancer growth? Med Hypotheses 33, 95-106 (1990).
7 Retsky, M. W., Swartzendruber, D. E., Bame, P. D. & Wardwell, R. H. A new paradigm for breast cancer. Recent Results Cancer Res 127, 13-22 (1993).
8 Retsky, M. W. et al. Computer simulation of a breast cancer metastasis model. Breast Cancer Res Treat 45, 193-202 (1997).
9 Lokich, J. & Anderson, N. Infusional cancer chemotherapy: historical evolution and future development at the Cancer Center of Boston. Cancer Invest 13, 202-226 (1995).
10 Ribatti, D. Judah Folkman, a pioneer in the study of angiogenesis. Angiogenesis 11, 3-10, doi:10.1007/s10456-008-9092-6 (2008).
11 Browder, T. et al. Antiangiogenic scheduling of chemotherapy improves efficacy against experimental drug-resistant cancer. Cancer Res 60, 1878-1886 (2000).
12 Romiti, A., Falcone, R., Roberto, M. & Marchetti, P. Current achievements and future perspectives of metronomic chemotherapy. Invest New Drugs 35, 359-374, doi:10.1007/s10637-016-0408-x (2017).
13 Rajasekaran, T. et al. Metronomic chemotherapy: A relook at its basis and rationale. Cancer Lett 388, 328-333, doi:10.1016/j.canlet.2016.12.013 (2017).
14 Kopans, D. B. The effect of changes in tumor size on breast carcinoma survival in the U.S.: 1975-1999. Cancer 106, 1863; author reply 1864, doi:10.1002/cncr.21805 (2006).
15 Elkin, E. B., Hudis, C., Begg, C. B. &Schrag, D. The effect of changes in tumor size on breast carcinoma survival in the U.S.: 1975-1999. Cancer 104, 1149-1157, doi:10.1002/cncr.21285 (2005).
16 Demicheli, R. et al. Local recurrences following mastectomy: support for the concept of tumor dormancy. J Natl Cancer Inst 86, 45-48 (1994).
17 Retsky, M. et al. Hypothesis: Induced angiogenesis after surgery in premenopausal node-positive breast cancer patients is a major underlying reason why adjuvant chemotherapy works particularly well for those patients. Breast Cancer Res 6, R372-374, doi:10.1186/bcr804 (2004).
18 Baum, M., Demicheli, R., Hrushesky, W. & Retsky, M. Does surgery unfavourably perturb the "natural history" of early breast cancer by accelerating the appearance of distant metastases? Eur J Cancer 41, 508-515, doi:10.1016/j.ejca.2004.09.031 (2005).
19 Demicheli, R., Retsky, M. W., Hrushesky, W. J. & Baum, M. Tumor dormancy and surgery-driven interruption of dormancy in breast cancer: learning from failures. Nat ClinPract Oncol 4, 699-710, doi:10.1038/ncponc0999 (2007).
20 Demicheli, R., Retsky, M. W., Hrushesky, W. J., Baum, M. &Gukas, I. D. The effects of surgery on tumor growth: a century of investigations. Ann Oncol 19, 1821-1828, doi:10.1093/annonc/mdn386 (2008).
21 Retsky, M., Demicheli, R., Hrushesky, W., Baum, M. &Gukas, I. Surgery triggers outgrowth of latent distant disease in breast cancer: an inconvenient truth? Cancers (Basel) 2, 305-337, doi:10.3390/cancers2020305 (2010).
22 Miller, A. B., To, T., Baines, C. J. & Wall, C. The Canadian National Breast Screening Study-1: breast cancer mortality after 11 to 16 years of follow-up. A randomized screening trial of mammography in women age 40 to 49 years. Ann Intern Med 137, 305-312 (2002).
23 Bross, I. D. & Blumenson, L. E. Screening random asymptomatic women under 50 by annual mammographies: does it make sense? J Surg Oncol 8, 437-445 (1976).
24 Retsky, M., Demicheli, R. &Hrushesky, W. J. Does surgery induce angiogenesis in breast cancer? Indirect evidence from relapse pattern and mammography paradox. Int J Surg 3, 179-187, doi:10.1016/j.ijsu.2005.08.002 (2005).
25 Forget, P. et al. Do intraoperative analgesics influence breast cancer recurrence after mastectomy? A retrospective analysis. AnesthAnalg 110, 1630-163 doi:10.1213/ANE.0b013e3181d2ad07 (2010).
26 Retsky, M. et al. NSAID analgesic ketorolac used perioperatively may suppress early breast cancer relapse: particular relevance to triple negative subgroup. Breast Cancer Res Treat 134, 881-888, doi:10.1007/s10549-012-2094-5 (2012).
27 Retsky M and Demicheli R (eds), Perioperative Inflammation as Triggering Origin of Metastasis Development, Springer Nature, Cham, Switzerland (2017).

Deciphering Ancestral Clues to a Subset of Metastatic Cancers

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Introduction: Racial Differences in Calcium Metabolism

African-Americans show an unusually high susceptibly to Metastatic Prostate Cancer (PCa) with a mortality rate 250% higher than that of their White counterparts. This ethnic population also has more than twice the mortality rate of Whites from Triple Negative Breast Cancer (TNBC), Ovarian and Colorectal Cancer. What these malignancies have in common is the tell-tale upregulation of mRNA from the TRPV6 calcium ion channel, which correlates with the advanced stages of prostate, colon, breast and ovarian carcinomas. The study of black vulnerability to these aggressive cancers uncovers their shared etiology and thus offers potential therapeutic targets that can be applied to patients of all ethnicities.

African-Americans are an admixed genetic population composed primarily of 75% Niger-Kordofanian West Africans, 24% Northern Europeans and 1% Native Americans. It is the African portion of this genetic ancestry that offers new insights into metastatic cancers. This is because of the oncogenic hypersensitivity to excess calcium of the African TRPV6a calcium ion channel variant when placed under environmental stresses. Because this allele is far more calcium-absorbent than the non-African//European TRPV6b variant, what might be the triggering mechanisms for such "stress"?

The Niger-Kordofanian (NK) genetic ancestors of Black Americans inhabit a vast swathe of West Africa infested by the parasitic tsetse fly (Glossina), the carrier of Trypanosoma brucei. Its presence represented for millennia a barrier to the introduction of pastoralism and dairy farming into these regions of the African continent. However, the NK populations maintained strong bones and low rates of osteoporosis on a 200-400 mg daily intake of dietary calcium, because the African TRPV6a variant absorbed more Ca2+ than the non-African TRPV6b variant.

While adaptive for NK populations inhabiting a low-calcium homeland, this TRPV6a variant may, however, have become more problematic, or even oncologically maladaptive for African-Americans in the high calcium, dairy food culture of the U.S. Even though this ethnic group is generally lactase non-persistent (lactose intolerant), the availability of popular low-lactose dairy products, such as ice cream, butter, yogurt and cheese in the diets, triples Blacks' calcium intake over that of their ancestors. A chronic flooding of excess free-calcium ions into prostatic and breast and among tissues that cannot be excreted in the urine, might in fact trigger the carcinogenic reaction of the more calcium-absorbent TRPV6a variant. This is because it works in concert with another variant. The African A563T Single Nucleotide Polymorphism found on the TRPV5 located in the kidneys retains excess calcium rather than expelling it in the urine, which occurs as a function of the non-African variant.

TRPV6-Expressing Cancers

Even apart from the high African-American risk of Metastatic PCa, an increasing number of reports have identified the over-consumption of calcium as a possible trigger for this disease. TRPV6 mRNA becomes a veritable biomarker for these malignancies as it proliferates in the prostate, breast or other organs and metastasizes. Recent investigations of ionized calcium at the cellular level have shown that a chronic excess can lead to disturbances in organelles, including the initiation of nuclear DNA mutations. The greater the exposure of the TRPV6 intestinal channel to Ca2+ (in the absence of alleles blocking its intestinal absorption), the higher the risk of producing mutagenic changes in the prostatic TRPV6 calcium ion channel.

Black women find themselves at an even more serious disadvantage. Because white females in the U.S. consume 43% more calcium than their African-American counterparts, the latter group is seen in contrast as "calcium deficient". No allowance is given to the fact that black women have strong bones and the lowest rate of osteoporosis of any American ethnic group. All American women are given the same public health message, which is to take supplemental calcium to strengthen their bone health. The nutritional guidelines do not take into consideration the fact that this ubiquitous advice might trigger metastatic cancers in females who carry the more calcium-absorbent TRPV6a gene variant.

A Potential Therapeutic Target

Even though the focus of this research is the TRPV6 calcium ion channel, the aim here is not to over-simplify the complex mechanism of calcium homeostasis. TRPV6 expression is also linked to the Vitamin D receptor (VDR). In addition, the "African" Q1011E allele (rs1801726 SNP) is found on the Calcium Sensing Receptor (CaSR) Gene, which modulates extracellular calcium homeostasis through secretion from the parathyroid hormone. This variant has also been linked to the bony metastases of

breast and prostate cancer. In short, it is not known which of these gene variants might independently or in concert with the TRPV6a variant contribute to blacks' higher susceptibility to these metastatic cancers. However, the TRPV6 channel has been singled out in this study because:

a. it represents the first step in the absorption of free-calcium ions into the small intestine;
b TRPV6 mRNA is dramatically over-expressed in metastatic tumors
c. this calcium ion channel can be blocked without interrupting cardiac and other vital functions.

At present, there is only one peptide TRPV6 inhibitor that successfully completed a phase I clinical trial in February 2016 to evaluate safety and tolerability. It is in the process of initiating phase II testing of the efficacy of the drug on solid tumors. The drug being tested, SOR-C13, is a compound derived from the venom of the northern short-tail shrew.

While lidocaine is commonly known as a local anesthetic, researchers at Chongqing Medical University in China announced their initial success in using the drug as a TRPV6 calcium channel blocker. The experiment was conducted in 2016, treating human breast cancer MDA-MB-231 cells, prostatic cancer PC-3 cells and ovarian cancer ES-2 cells with lidocaine in a concentration-dependent manner between 1 and 10 mM. Lidocaine decreased cell viability, and inhibited migration and invasion in all these cell lines. Since then, several new investigations have been launched and await results regarding the use of lidocaine to suppress lung cancer, hepatocellular carcinoma, bladder and prostate cancer.

References

1 V Lehen'kyi, M Raphaël, N Prevarskaya. The role of the TRPV6 channel in cancer. J Physiol. 2012 Mar 15; 590(Pt 6): 1369–1376.
2 C Hilliard. High osteoporosis risk among East Africans linked to lactase persistence genotype. BoneKEy Reports 5, 803 (2016)
3 L Wang, RP Holmes, JB Peng. Molecular Modeling of the Structural and Dynamical Changes in Calcium Channel TRPV5 Induced by the African-Specific A563T Variation. Biochemistry. 2016.55. 1254-1264.
4 E Lastraioli, J Iorio, A Arcangeli. Ion channel expression as promising cancer biomarker. Biochimica et Biophysica Acta (BBA) – Biomembranes. Volume 1848, Issue 10, Part B, October 2015, Pages 2685-2702
5 C Cárdenas et al. Selective Vulnerability of Cancer Cells by Inhibition of Ca2+ Transfer from Endoplasmic Reticulum to Mitochondria. Cell Reports , Volume 14 , Issue 10 , 2313 – 2324
6 K Plawecki, E Evans, M Mojtahedi; E McAuley, K Chapman-Novakofski, Assessing Calcium Intake in Postmenopausal Women. Preventing Chronic Disease: Public Health Research, Practice and Policy.Volume 6: No. 4, October 2009
7 K. Alaimo, M McDowell, R Briefel, A Bischof, C Caughman, C Loria, C Johnson. Dietary intake of vitamins, minerals, and fiber of persons 2 months and over in the United States: Third National Health and Nutrition Examination Survey, Phase 1, 1988–91. Advance data from vital and health statistics; no. 258. Hyattsville, Maryland: National Center for Health Statistics. 1994.
8 H Skinner, G Schwartz. The Relation of Serum Parathyroid Hormone and Serum Calcium to Serum Levels of Prostate-Specific Antigen: A Population-Based Study. Cancer Epidemiol Biomarkers Prev. 2009 Nov;18(11):2869-73
9 C Bowen, D DeBay, H Ewart, P Gallant, S Gormley, T Ilenchuk . In vivo detection of human TRPV6-rich tumors with anti-cancer peptides derived from soricidin. PLoS One. 2013;8(3):
10 Y Jiang, H Gou, J Zhu, S Tian, L Yu . Lidocaine inhibits the invasion and migration of TRPV6-expressing cancer cells by TRPV6 downregulation. Oncology Letters. 2016;12(2):1164-1170.

Kurt Hellman – a rare breed of medical and scientific humanitarian

Kurt Hellman
(May 12, 1922 April 2, 2013)

Driven by a desire to know what is beyond the horizon led the UK clinician and pharmacologist Kurt Hellmann to discovery of the unique cytotoxic, cytoprotective and antimetastatic acivities of bisdioxopiperazines in his laboratory at ICRFF's Cancer Chemotherapy Unit in London in the early 1970's. Following Karrer, Goldin and Humphrey's description of the Lewis lung (3LL) carcinoma as a model for metastases, Hellmann set up 3LL as a screen for antimetastatic compounds in 1968. The first compound to be tested in this antimetastatic drug screen was the cytostatic agent DL-razoxane (ICRF-159). As serendipity would have it, DL-razoxane showed almost total suppression of metastases without seeming to affect the growth of the primary implant, thus making DL-razoxane the first fully antimetastatic compound. This work was regarded as a major breakthrough when published in a landmark paper in the BMJ on March 4, 1972 (1). Hellmann clearly showed that a drug which normalised the tumour-induced pathologic vasculature prevented lethal metastasis. Such an observation pre-dated by many years the current interest in the conversion of tumour vasculature to a more normal morphology and function as a therapeutic approach (2), even in the emerging field of immuno-oncology (3). This biomedical discovery led Denys Wheatley further to muse on 'rediscovery in science' and ways, we might reduce the many claims of "new" discoveries that seem to be of considerable significace but are in fact rediscoveries (4).

By serendipitous coincidence of time and circumstances Hellmann had in the early seventies begun a collaboration with the US National Cancer Institute (NCI) to examine the unusual antitumour properties of this cyclised form of EDTA synthesised by the ICRF chemist, Andrew Creighton (5), when Eugene Herman working at Abraham Goldin's lab had independently discovered the cardioprotective effect of EDTA in his models. It was also found that DL-razoxane, and subsequenly the less toxic but much more soluble D-razoxane (dexrazoxane, ICRF-187), was highly effective in preventing anthracycline-mediated cardiotoxicity and treating accidental anthracycline extravasation. The fascinating story can be found in the monograph edited by Hellmann and Rhomberg: "Razoxane and Dexrazoxane - Two Multifunctional Agents" in 2011 (6). In the case of prevention of anthracycline cardiotoxicity by dexrazoxane Hellmann was driven by the desire what is beyond the barrier of the dose-limiting toxicity of anthracyclines. For doxorubicin with its broad spectrum of antitumour activity, as well as other anthracyclines, an irreversible, cumulative, destructive cardiomyopathy restricts full exploration of the antitumor effects of these drugs. The first demonstration of the cardioprotective effect of bisdioxopiperazines by classical pharmacology methods in the isolated dog heart was described by Herman in 1972 (7) the very year of Hellmann's BMJ publication on metastasis prevention! There was consistency of protective effect in all of the in-vivo animal species tested (8) which rapidly led to clinical trials in the US and in Europe in the early 1990's- first in adult breast cancer patients and subsequently in children with sarcoma and acute lymphoblastic leukaemia (ALL) (9).

Kurt Hellmann - with astonishing foresight - pointed out that pharmacological anthracycline cardiotoxicity prevention will increasingly become important for mainaining the quality of life of cured long-term survivors

Currently dexrazoxane is the only FDA/EMA approved agent for preventing anthracycline cardiotoxicity which according to James Doroshow (NCI) should become an essential part as a protective agent in anthracycline-containing treatament schedules (10). In Circulation Research 29 March 2018, the pediatric cardiologist, Steven Lipshultz, responsible for many important primary and secondary prevention studies in cardio-oncology, published an update of the European Union label for dexrazoxane which, allows virtually all children to receive dexrazoxane starting with the first dose of anthracycline at the discretion of the treating provider without reducing its oncologic efficacy, even allowing safer anthracycline dose escalation' to keep the responders responding (11). In his JCO-editorial back in 1996 Kurt

Hellmann - with astonishing foresight - pointed out that pharmacological anthracycline cardiotoxicity prevention will increasingly become important for mainaining the quality of life of cured long-term survivors, especially for children with ALL whose cure rate now approaches 85-90%.

These two breakthroughs in translational metastasis research and ameliorating cancer drug toxicity are embedded in Kurt Hellmann's long life as a well-respected oncologist and researcher. He remained active as a writer, discussant, advisor and benefactor until the very end of his remarkable and productive life encouraging young investigators and giving them opportunities. His last letter to the editor of the Journal of Clinical Oncology was published just weeks before his death (12).

As head of Chemotherapy at ICRF, he also had an honorary professorship in Radiotherapy at the Westminster Hospital

Kurt Hellmann was born in Nürnberg, Bavaria, on 12 May 1922, where he attended primary school from 1927 to 1932 and the first year of the 'Reformgymnasium' before having to emigrate as a 10-year-old boy with his parents and his elder brother to England in March 1933. On leaving school he worked as a lathe turner in a tool factory but, although this opened his eyes to the dismal home and working conditions of some of his workmates, which roused his socialist instincts, it didn't satisfy his intellectual curiosity. In the evenings he studied, well into the night, as an external student at Imperial College London and earned a B.Sc. in Chemistry. He accepted a post with a group at the MRC to help in a study of the effect of heat on men in various situations e.g. submarines. Initially due to go to Singapore, conditions dictated otherwise. The group was sent instead to the Anatomy Dept. at Oxford to work with Prof. Le Gros Clark. While there he met and made friends with Dr. Joe Weiner who was instrumental in debunking the authenticity of Piltdown Man. While in Oxford he did a D.Phil. in Pharmacology at Magdalen College (1953). Having learned about drugs he felt it was pointless not to know how they actually affected people. He therefore decided to do medicine. Because Magdalen had already got its full quota of medical students for the year he became a student at Balliol. As a student, financial assistance was gained by doing a few hours/week teaching mathematics to a ground crew at one of the USAF bases near Oxford – an amazing and amusing experience. He qualified B.M.ChB. in 1958. D.M. in 1964 with the prestigious Radcliffe Prize for Medical Research for his histochemical investigations on cholinesterase and amine oxidase in the skin. Having qualified he did both his medical and surgical pre-registration house jobs at the Radcliffe Infirmary and it was there during 1959 he met Jane who was doing a year as resident pathologist. At the end of July 1961 they were married at Chelsea Registry Office. He then joined Reckitt & Sons, Hull, to lead its Department of Pharmacology but was seconded to undertake medical research at the Department of Pharmacology, Royal College of Surgeons, London. In 1962 he became Director of the newly formed Department of Cancer Chemotherapy at the Imperial Cancer Research Fund London (ICRF; now the Cancer Research UK London Research Institute)- a post which he held until 1987.While head of Chemotherapy at I.C.R.F. he also had an honorary professorship at the Radiotherapy Dept. of the Westminster Hospital (now Imperial College) from 1972 to 1993. This was probably the most satisfying period of his life – combining research, seeing patients and working with colleagues, radiotherapist and surgeons whom he liked and for whom he had the greatest respect. Indeed it was a sad day when the Westminster Hospital closed.

Kurt Hellmann - with astonishing foresight - pointed out that pharmacological anthracycline cardiotoxicity prevention will increasingly become important for mainaining the quality of life of cured long-term survivors

In March 1974, Kurt Hellmann founded with his co-editor Stephen Carter (Director of the Division of Cancer Treatment, US National Cancer Institute) the highly regarded journal 'Cancer Treatment Reviews' which he edited from volume 1(1), 1974 to volume 18(4) in December 1991. With Stephen Carter he published 'Chemotherapy of Cancer' in 1977 a convenient reference and guidebook for practising medical oncologists which ran through several editions. In March 1974 he organized the first meeting of the E.O.R.T.C. Metastasis Club which he founded together with Silvio Garattini, Director of the Mario Negri Institute for Pharmacological Research, Milan. In the early 1980s the ever-expanding interest in the field of metastasis led to the 'Metastasis Research Society'. Its first international meeting was organised by Kurt Hellmann

and Suzanne Eccles in London, in 1984 shortly after the inauguration of the Society's official journal 'Clinical & Experimental Metastasis' with Kurt Hellmann and co-editor Garth Nicolson.

In 1972 Kurt Hellmann acted as Chairman of the British Association of Cancer Research (BACR) and gave the 'Erasmus Wilson Lecture' of the Royal College of Surgeons. When the Queen opened a new wing at ICRF's Lincoln's Inn site in 1973 he was given the task of showing her around the Department of Cancer Chemotherapy in which she took great interest. Following the Royal visit he received an invitation to lunch at the Palace. Some 10 years later, as President of the Oncology Section of the Royal Society of Medicine, London, he was invited to give the 'Haddow Lecture' of BACR. Kurt Hellmann also made an memorable debut in 'A Career in Pharmacology' in 1961 filmed by members of staff of the Department of Pharmacology at the Royal College of Surgeons of England,then based at Examination Hall, Queen Square London, co-starring with the later Nobel Prize winner John Vane and others (13). The Wellcome Library also holds a recording of a 1993 interview between Kurt Hellmann and two other colleagues remembering Sir Stanford Cade (1895–1973). Cade was a pioneer in radiotherapy at the Westminster Hospital and an Air Vice Marshall of the Royal Airforce whose invaluable collection of case summaries was rescued by Hellmann upon the closure of the Westminster Hospital and given to the Contemporary Medical Archives Centre of the Wellcome Trust's Library (GC147). The published proceedings of 'The Stanford Cade Symposium' organized by Kurt Hellmann at the Royal Institution, London, in 1973 bear witness to his early interests in preserving our medical heritage.

As he grew older, Kurt Hellmann's socialist instinct became rather staunchly conservative. He was a great admirer of Churchill. In his younger days he had played tennis and squash quite well. He was interested in Oriental Art and classical music and he greatly admired the Arts & Craft movement and became a particular fan of the architect W.A.S. Benson, whose house in East Sussex was home for the last 35 years of his life. Kurt Hellmann died on 2 April 2013 at the age of 90 in Withyham, East Sussex, UK.

A fuller acount of Professor Hellmann's life and career was published as a 90th birthday tribute in Clinical & Experimental Metastasis in 2012 (14). I would like to express my gratitude to Jane Hellman for contributions and memories.

References

1. Br Med J. 1972;1(5800):597-601; reprinted in: Clin Exp Metastasis. 2008;25(4):283-8.
2. Editorial ON 12(1),March/April2017.
3. Nat Immunol. 2017 Nov;18(11):1207-1217.
4. Ecancermedicalscience. 2018 Feb 12;12:ed79. doi: 10.3332/ecancer.2018.ed79. eCollection 2018.
5. Nature.1969; 26;222:384-5.
6. ISBN:978-90-481-9167-3.
7. Proc Soc Exp Biol Med. 1972;140(1):234-9.
8. Cardiovasc Res. 2018 Feb 1;114(2):205-209.
9. Ecancermedicalscience. 2014 May 29;8:433. doi: 10.3332/ecancer.2014.433.
10. Curr Pharm Biotechnol. 2012;13(10):1949-56.
11. Circ Res. 2018 Mar 30;122(7):e62-e63. doi: 10.1161/CIRCRESAHA.118.312918.
12. J Clin Oncol. 2013:1;31(10):1379.
13. A Career in Pharmacology, 1961. Wellcome Trust, re-edited DVD, 2009.
14. http://link.springer.com/content/pdf/10.1007%2Fs10585-012-9513-1

[N.B. Oncology News will in future include articles on people who have made significant contributions to our understanding on the disease and its treatment. While there have been hundreds, many of whom have been particularly outstanding (e.g. Charles Huggins received a Nobel Prize in 1967), we will try to feature those whom you (our readers) would like to portray. To submit, please send entries to editor@oncologynews.biz]

Decellularized Matrices (DCMs) for Material Sciences and Tissue Engineering

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Our university in Erlangen-Nuremberg together with other German universities has recently been awarded a grant from the German Science Foundation on the bio-fabrication, i.e. the use of 3D printing techniques to simultaneously process living cells and biomaterials (hydrogels) to mimic complex tissue and organ-like 3D structures. The goal of this long-term research funding is to investigate how decellularized biological tissue, such as the microarchitecture and protein content of the matrix, are conserved. Research will focus on particular organs (e.g. bone, heart, etc.) to apply the knowledge gained to matrices that ideally preserves the structure and composition of the native extracellular matrix (ECM). Following biochemical, histological, mechanical and structural analyses to identify the best procedure to ensure complete cell removal, while preserving most of the native ECM structure and composition, the researchers plan to develop a bioactive product. In all research efforts, biocompatibility, biodegradability and bioinductivity of DCMs are important factors, which need to be considered in surgical practice (implantation) and research (tissue engineering and material sciences).

After establishing the use of the appropriate matrices, the 3D fabrication process will be started and different techniques such as prototype printing or conventional mold or stereo-lithographic methods will be employed. A mixture of hydrogel and specific cells will be used to coat the scaffold made from synthetic biomaterials, which are now commonly used in the field of bioengineering and regenerative medicine. In some specific cases, stem cells will be tested as these have the tendency to differentiate into cell types suitable for DCMs. Thus, all forms of DCMs will be used and studied to reveal their potential role in regenerating functional tissue.

The utilization and naturalisation of delivered factors and natural growth of cells without any host immune response are the main concern for successful tissue engineering. Researchers are confident that an ideal 3D DCM scaffold can be generated for functional tissue regeneration and restoration of a functional organ after grafting in the near future. For further reading on this topic, see references [1-8].

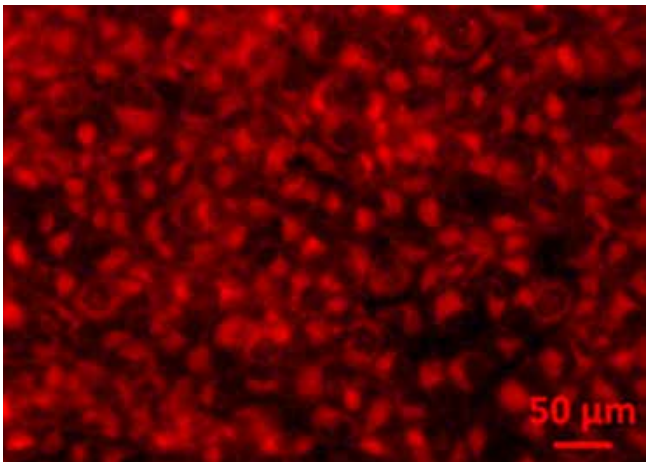

Figure 1: *Cu-releasing bioactive glass/polycaprolactone coatings on human osteosarcoma cells (MG-63; Sigma-Aldrich) used for in vitro cell biocompatibility assessments and bone tissue engineering. Vybrant®Dil stained cells are shown here after 72 h of cultivation. Note, bioactive glass nanoparticles containing copper (Cu-BGNs) were introduced into polycaprolactone coating systems to improve the bioactivity, antibacterial properties, and corrosion resistance of vulnerable magnesium matrices under physiological conditions [9]. The image was taken with the permission of IOP Publishing.*

> biocompatibility, biodegradability and bioinductivity of DCMs are important factors, which need to be considered

Although many disease models have been described, cancer cell invasion, progression, and their survival and establishing metastases in a microenvironment is currently not well understood and remains one of the most challenging topics in cancer treatment. Therefore, to closely mimic the tumour microenvironment, studies are geared to developing a 3D bioengineered in vitro bone model for the study of bone metastasis [9]. The editor, in a timely way, had introduced this topic in the last issue of Oncology News [10].

Acknowledgments and funding

I thank Liz Nicholson (MA) for proofreading the manuscript. This work was supported by grants from German Science Foundation (DFG, Go598).

References

1. Vaquette C et al. Effect of culture conditions and calcium phosphate coating on ectopic bone formation. Biomaterials 34, 5538-5551, 2013.
2. Thibaudeau L et al. A tissue-engineered humanized xenograft model of human breast cancer metastasis to bone. Disease models and mechanisms 7, 299-309, 2014.
3. Shevach M et al. Gold nanoparticle-decellularized matrix hybrids for cardiac tissue engineering. Nano Letters 14, 5792-5796, 2014.
4. Sutherland AJ et al. Decellularized cartilage may be a chondroinductive material for osteochondrial tissue engineering. PLUS One 0121966, 2015.
5. Welman T et al. Bioengineering for organ transplantation: progress and challenges. Bioengineered 6, 257-261, 2015.
6. Fitzpatrick LE et al. Cell-derived matrices for tissue engineering and regenerative medicine applications. Biomaterial Sciences 3, 12-24, 2015.
7. Hoshiba T et al. Decellularized extracellular matrix as an in vitro model to study the comprehensive roles of ECM in stem cell differentiation. Stem Cells International, 6397820, 2016.
8. Ahn G et al. Precise stacking of decellularized extracellular matrix based 3D cell-laden constructs by a 3D cell printing system equipped with heating modules. Scientific Reports 7, 8624, 2017.
9. Yang Y et al. Cu-releasing bioactive glass/polycapro-lactone coating on Mg with antibacterial and anticorrosive properties for bone tissue engineering. Biomedical Materials 13, 015001, 2017.
10. Wheatley D N. Decellularised Matrices (DCMs) – a new method of following stroma-v-cell interactions. Oncology News 13, 4, 2018.

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April 18-20, 2018
British and Irish Association of Robotic Gynaecological Surgeons
8th Annual BIARGS Conference
The Veterinary School MAIN Building (VSM)
Daphne Jackson Road
Guildford, Surrey, GU2 7AL
biargs2018guildford@gmail.com

May 1-3, 2018
Cancer Research UK
Brain Tumour Conference
The Royal Society of Medicine
1 Wimpole Street, Marylebone, London W1G 0LZ
brainconference@cancer.org.uk

May 3-5, 2018
The 4th World Congress on CONTROVERSIES IN MULTIPLE MYELOMA (COMy)
Novotel Tour Eiffel Hotel
61 quai de Grenelle
Paris, France 75015
comy@cme-congresses.com

May 24-25, 2018
2nd International Conference on Cancer Genetics and Epigenetics
Tokyo, Japan
worldepigenetics@cancersummit.org

May 24-25, 2018
22nd Global Annual Oncologists Meeting
Osaka, Japan
oncologistsmeet@cancersummit.org

May 28-29, 2018
World Haematology and Medical Oncology Conference
Osaka, Japan
medicaloncology@conferencesworld.org

June 1-5 , 2018
AMERICAN SOCIETY OF CLINICAL ONCOLOGY
54th ANNUAL MEETING 2018
McCormick Place
Chicago, IL
info@asco2018.com

June 1-2, 2018
Global Meeting on Oncology and Radiology
Osaka, Japan
clinicaloncology@conferencesworld.org

June 25-26, 2018
Cancer Genomics Conference: New Era For Cancer Prevention
Dubai, UAE
cancergenomics@cancersummit.org

June 26-28, 2018
Armed Oncolytic Immunotherapy Summit
E: info@hansonwade.com
Le Méridien Frankfurt
Wiesenhuettenplatz 28-38
Frankfurt, 60329
Germany

July 1-4, 2018
Beatson International Cancer Conference
Understanding the Biology of the Metastatic Niche
Glasgow, Scotland
conference@beatson.gla.ac.uk

July 02-03, 2018
World Cancer Summit 2018
Bangkok, Thailand
worldcancersummit@annualcongress.net

July 16-17, 2018
International Conference on Biomarkers and Cancer Targets
Dubai, UAE
biomarkers@cancersummit.org

July 18-19, 2018
4th Annual Conference on Preventive Oncology
Atlanta, Georgia, USA
Preventiveonco@oncologyseries.com

July 18-19, 2018
4th Annual Conference on Gynecologic Oncology and Reproductive Disorders
Atlanta, Georgia, USA
gynecologiconcology@oncologyseries.com

July 23-25, 2018
29th Euro-Global Summit on Cancer Therapy & Radiation Oncology
Rome, Italy
eurocancer@oncologyseries.com

July 23-24, 2018
Experts Meet on Cancer Therapy 2018
Melbourne, Australia
cancertherapy@annualcongress.net

August 02-03, 2018
14th Global Biomarkers Summit
Oslo, Norway
biomarker@healthconferences.org

September 5-6, 2018
15th Asia Pacific Oncologists Annual Meeting
Tokyo, Japan
globalcancer@oncologymeet.com

August 09-10, 2018
8th World Conference on Women's Health and Breast Cancer
Abu Dhabi, UAE
breastcancer@healthconferences.org

August 09-10, 2018
28th Euro Congress on Cancer Science & Therapy
Madrid, Spain
cancerscience@oncologyseries.com

August 30-31, 2018
Head and Neck Oncology Conference: Precaution and Treatment
Dubai, UAE
headneck@oncologymeeting.org

September 03-05, 2018
4th International Congress on Epigenetics & Chromatin
London, UK (Park Inn By Radisson London Heathrow)
epigenetics@conferenceseries.net

September 17-18, 2018
International Conference on Oncogenesis and Oncologic Emergency Medicine
San Diego, California, USA
oncologenesis@americaconferences.com

September 17-18, 2018
28th International Conference on Cancer Research and Anticancer Therapies
San Diego, California, USA
cancer@americaconferences.com

September 20-21, 2018
3rd Cancer Diagnostics Conference & Expo
Berlin, Germany
cancerdiagnostics@oncologyseries.com

September 27-28, 2018
3rd World Conference on Breast and Cervical Cancer
Abu Dhabi, UAE
breastcervical@oncologymeeting.org

October 03-04, 2018
12th World Congress on Biomarkers & Clinical Research
Los Angeles, California, USA
biomarkers@oncologyseries.com

October 03-04, 2018
2nd International Conference on Cancer Biology and Drug Delivery
Los Angeles, California, USA
cancerbiology@oncologyseries.com

August 2-3 2018
International Conference on Cancer Diagnosis & Treatment
Oslo, Norway
cancertreatment@healthconferences.org

October 8-9, 2018
International Conference on Molecular Markers and Cancer Therapeutics
Dubai, UAE
rohit.casper@healthcarevents.com

October 15-16, 2018
22nd World Conference On Liquid Biopsy & Biomarkers
Toronto, Canada

October 17-18, 2018
Annual Congress on Cancer and Stem Cell Research
New York, USA
cancerstemcells@americaconferences.org

October 18-19, 2018
Euro Oncology Summit
Amsterdam, Netherlands
eurooncology@cancersummit.org

October 18-19, 2018
Euro Breast Cancer Summit
Amsterdam, Netherlands
rajeshguru@conferencesseries.com

October 22-24, 2018
5th World Congress on Epigenetics and Chromosome , Turkey
rohit.casper@healthcarevents.com

August 1-2, 2018
International Conference on Cancer Science & Robotics
Melbourne, Australia
roboticsurgery@annualcongress.net

October 11-13, 2018
36th World Cancer Conference
Zurich, Switzerland
worldcancer@annualconferences.org

October 26-27, 2018
International Conference on Robotic Oncology
Osaka, Japan
oncorobotics@annualcongress.net

October 29-30, 2018
26th Annual Congress on Cancer Science and Targeted Therapies
San Francisco, California, USA
cancertherapy@cancersummit.org

October 29-30, 2018
International Conference on Gastrointestinal Cancer and Therapeutics
San Francisco, California, USA
gicancer@americaconferences.com

November 29-30, 2018
13th World Biomarkers Congress
Dublin, Ireland
worldbiomarkers@annualconferences.org

December 07-08, 2018
27th World Oncologists Annual Conference
Chicago, Illinois, USA
oncology@conferencesamerica.org

September 27-28, 2018
3rd World Conference on Breast and Cervical Cancer
Abu Dhabi, UAE
breastcervical@oncologymeeting.org

October 03-04, 2018
12th World Congress on Biomarkers & Clinical Research
Los Angeles, California, USA
biomarkers@oncologyseries.com

October 03-04, 2018
2nd International Conference on Cancer Biology and Drug Delivery
Los Angeles, California, USA
cancerbiology@oncologyseries.com

August 2-3 2018
International Conference on Cancer Diagnosis & Treatment
Oslo, Norway
cancertreatment@healthconferences.org

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CANCER RESEARCH UK

BEATSON INTERNATIONAL CANCER CONFERENCE

Co-sponsor WORLDWIDE CANCER RESEARCH

"TALK TO THE NICHE – Understanding the Biology of the Metastatic Niche"

Sunday July 1st – Wednesday July 4th, 2018, Glasgow UK

KEYNOTE SPEAKER: Val Weaver (USA)

Mechanotransduction:
Janine Erler (Denmark), Xavier Trepat (Spain), Mike Olson (UK)

Extracellular Vesicles and Exosomes:
Alissa Weaver (USA), Jacco van Rheenen (Netherlands), Clotilde Théry (France), David Lyden (USA)

Microenvironment & Angiogenesis
Sara Zanivan (UK), Danijela Vignjevic (France), Max Mazzone (Belgium), Clare Isacke (UK), Claus Jorgensen (UK), Paul Timpson (Australia)

Non-Mammalian Models of Invasion and Metastasis
Will Wood (UK), Ross Cagan (USA), David Sherwood (USA)

Mammalian Models of Metastasis and Dormancy
Thomas Tüting (Germany), Greg Hannon (UK), Julio Aguirre-Ghiso (USA), Laura Machesky (UK), Dave Adams (UK)

Short talks will be granted to the authors of outstanding abstracts.
Some financial assistance will be available to the presenters of these talks through sponsorship from Worldwide Cancer Research

Website, on-line registration, payment and abstract submission instructions: **http://www.beatson.gla.ac.uk/conf**

For additional information please contact: **Conference Administrator,**
Beatson Institute for Cancer Research, Garscube Estate, Switchback Road, Bearsden, Glasgow, G61 1BD, UK
Tel: +44(0) 141 330 3953 Fax: +44(0) 141 942 6521 Email: conference@beatson.gla.ac.uk

Deadline for registration, payment and abstract submission: **Friday 11th May**

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