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Personalised Medicines

‘Personalised medicine’ through ‘personalised medicines’: Time to integrate advanced, non-invasive imaging approaches and smart drug delivery systems

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ABSTRACT

In this Commentary, the authors briefly discuss the status of efforts to individualize therapeutic interventions. They differentiate between the widely discussed idea of further shaping ‘personalized medicine’ approaches by using (new) biomarkers and (molecular) imaging techniques and the much less debated topic of ‘personalized medicines’: medicines, often carrier based, specifically geared to treat the individual patient optimally.

An example where ‘personalized medicine’ is achieved by ‘personalized medicines’ is described: a smart drug delivery system is activated at the target site by non-invasive radiation (focused ultrasonic radiation, FU) while this spatial and temporal release process is guided and monitored by MRI (Magnetic Resonance Imaging guided High Intensity Focused Ultrasonic, MRIgHIFU).

1. Personalized medicine

Personalized medicine means different things to different authors and readers. When discussing personalized medicine we prefer to use the following definition: Personalized medicine involves the systematic use of information about each individual patient to select or optimize the patient’s preventative and therapeutic care (http://en.wikipedia.org/wiki/Personalised medicine, September 2010).

Interest in personalized medicine is growing. Fig. 1, where data are shown from the Web of Science (search term ‘personalized medicine’ in the title) shows clear evidence for that. Moreover, the journal *Personalized Medicine* has existed for 6 years and a Textbook of Personalized Medicine was published last year (Jain, 2009).

But, if we reflect on the definition of personalised medicine above, one might wonder: what is new? Therapy always has been focused on the paradigm of categorising patients down to patient category and even the level of the individual patient. In the past, the drive to make therapy ‘personalized’ depended on the severity of the disease. Clear examples where treatment have been individual patient oriented are the choice of antibiotics in serious bacterial infections, the choice of antivirals in HIV therapy and the approach selected to treat different types of tumours. Treating regular headaches though, inconvenient as they may be, has not led to personalized treatment protocols.

However, times are changing with regard to personalization. Our diagnostic tools have improved and will continue to do so. On the one hand, molecular biology provides us with new tools to develop biomarkers, which will be widely used in therapy. Examples are the RNA/DNA microarray type of tests that are rapidly introduced and help to further rationalize and individualize treatment options. For example, the introduction of Mammaprint™ (http://www.agendia.com/pages/home/1.php, September 2010) not only provides a genetic fingerprint of breast tumour tissue, but the test also advises what further therapy is indicated for an optimum therapeutic outcome for the patient. Another example is assessment of the overexpression of the HER2 receptor in breast cancer tissue. The level of overexpression is critical for the decision to treat a patient with trastuzumab (Herceptin®), a monoclonal antibody directed at the extracellular domain of HER2. Other biomarker approaches are based on monitoring one particular marker molecule such a PSA (prostate specific antigen). PSA blood levels are being used to follow success of the treatment over time. Considering the enormous and still expanding efforts in research (Fig. 2, Metzler, 2010) one can expect that the use of biomarkers in drug design and development and also for optimizing therapeutic outcome in individual patients will continue to grow. As an example, recently Kho et al. (2010) reviewed the benefits of prognostic (outcome of disease without therapeutic intervention) and predictive (outcome of disease with such an intervention)

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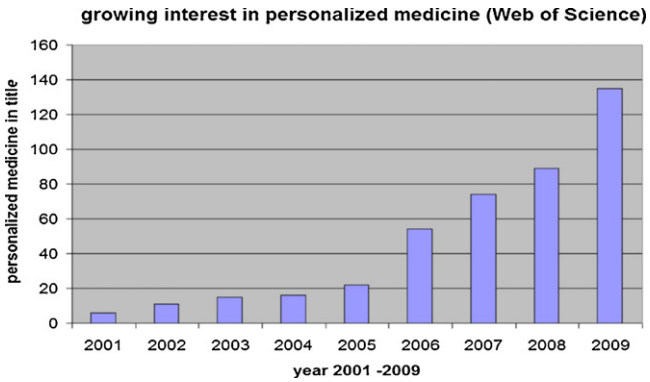

Fig. 1. Number of articles with 'personalized medicine' in the title (from the Web of Science).

biomarkers in the treatment of different types of cancer. In short, with an increasingly sophisticated armamentarium of diagnostic technologies all major pathologies may end up as classes of orphan diseases, each requiring a very specific treatment (Bernards, 2010).

1.1. Can we afford it?

An aspect that early on has received considerable attention in the context of personalized medicine is the pharmaco-economic side. In an excellent review Davis et al. (2009) discuss the critical role that regulatory bodies (e.g. EMA and FDA) and national payers/providers play in the successful introduction of advanced diagnostic tools to influence drug therapy. Their analysis emphasizes the importance of a sound economic rationale including the necessity of a long development and investment horizon for pharmaceutical and diagnostic companies to bring diagnostic agents that affect pharmacotherapeutic decisions to the market. They illustrate their analysis with a number of well chosen examples of success and failure. How this analysis will affect business models in the pharma industry depends, amongst other things, on the disease area. Cancer and infectious diseases are the obvious first candidates for an integrated approach (now known as theranostics).

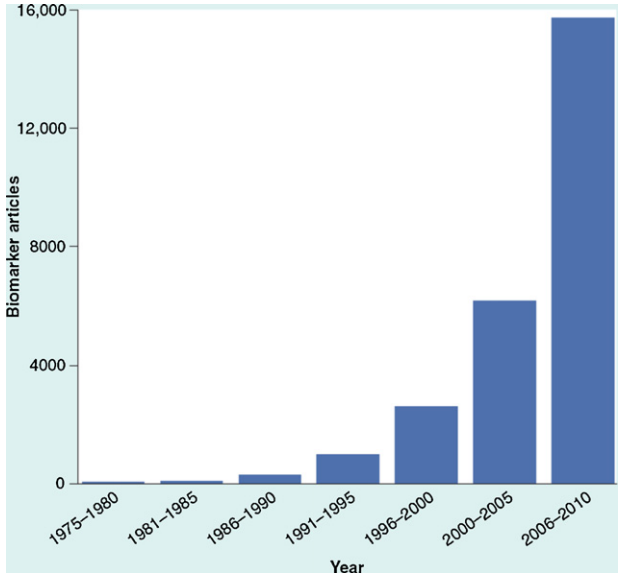

Fig. 2. The absolute numbers of 'biomarker articles' since 1975 in 5-year periods. The data are taken from the Scopus® database (Elsevier, Amsterdam, The Netherlands) and grouped in 5-year periods. Biomarker articles were defined as containing the term 'biomarker' in the title, abstract or keywords. Through Metzler (2010).

Table 1
Typical data on spatial resolution and sensitivity of five imaging techniques (cf Fass, 2008; Deckers et al., 2008; Riklund, 2010).

Imaging techniques	Spatial resolution	Sensitivity
MRI	<0.5 mm	Micromolar
CT	<0.5 mm	Millimolar
SPECT	4–12 mm	Nanomolar
PET	3–6 mm	Picomolar
Ultrasound	0.5 mm	Micromolar

Companies such as Roche have recognised this and marketed combinations of a diagnostic/drug combination (as with trastuzumab; Herceptin®).

1.2. What can (molecular) imaging techniques contribute to improve therapeutic interventions?

In the last decade, enormous progress has been made regarding new imaging techniques using different parts of the electromagnetic radiation spectrum. The MRI, CT, US (structural imaging, high resolution) and PET, SPECT (functional imaging, lower resolution) concepts are well accepted and appreciated in the clinical setting and in different stages of novel drug discovery, development and testing. Typical lower limits for spatial resolution and sensitivity for the five leading imaging approaches can be found in Table 1.

In the literature many 'promising' biomarkers are proposed. However, EMA and FDA still request full validation of imaging biomarkers as surrogate endpoint markers (Richter, 2006). As the identification of a validated biomarker is important for more than one company and the rising costs of validation are becoming prohibitive for one single company to pay for, public–private-partnerships (PPPs) have been formed where industry, regulatory authorities and academia work together to identify and validate biomarkers (Dutch Top Institute Pharma (TI Pharma, http://www.tipharma.com, September 2010), Dutch Center for Translational Medicine (CTMM, http://www.ctmm.nl, September 2010), the European Innovative Medicines Initiative (IMI, http://www.imi-europe.org, September 2010) and US Biomarkers Consortium (http://www.biomarkersconsortium.org, September 2010).

All these imaging techniques have their pros and cons (reviewed by Moyer and Barrett, 2009). New developments in these imaging techniques, such as DW-MRI (diffusion weighted), DCE (dynamic contrast-enhanced) MRI, and magnetic resonance spectroscopy (MRS) provide additional, more detailed insights (Fass, 2008; Harry et al., 2010; Van De Meel et al., 2010). Combination of outcomes from hybrid approaches involving MRI or CT and PET or SPECT ('multimodality imaging') further enhances the power of the predictive, diagnostic and/or prognostic analyses.

2. 'Personalized medicines'

There is a difference between the meaning of the term 'personalized medicine' and '*personalized medicines*'. The last term refers to *medicines* specifically focused on the individual patient. There is a sliding scale from 'mass oriented delivery systems' such as tablets, capsules and ointments via special dosage forms for categories of patients: children or the elderly patient (e.g. opening child-resistant containers, handling small tablets/capsules or swallowing conventional dosage forms) to highly specific, integrated treatment strategies where drugs are delivered in a temporal-spatial controlled manner.

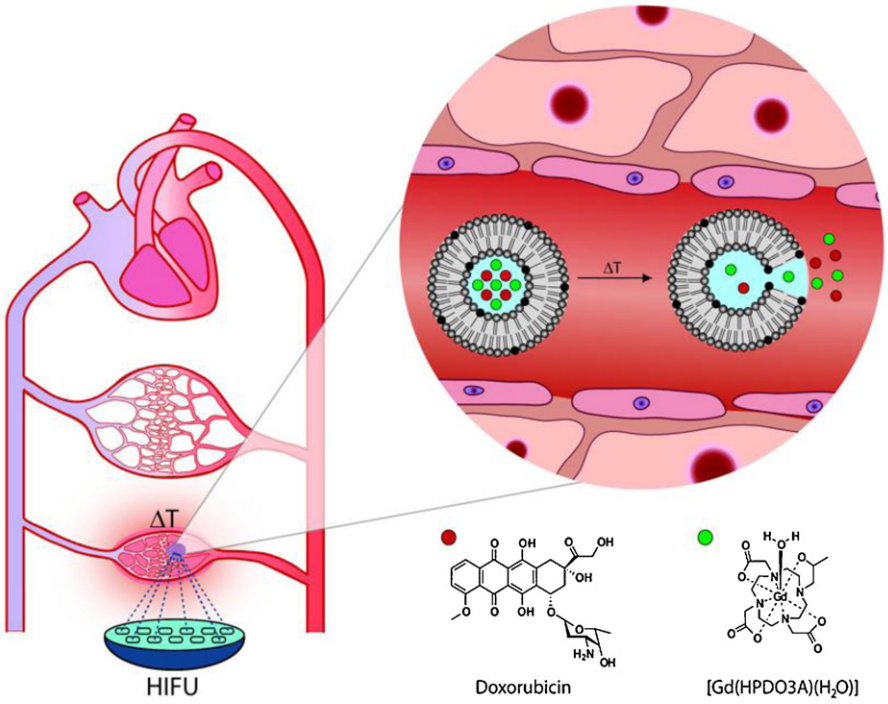

Fig. 3. Schematic representation of temperature-induced release from temperature sensitive liposomes containing doxorubicin (red dots) and [Gd(HPDO3A)(H2O)] (green dots). Local hyperthermia can be achieved non-invasively with HIFU under MRI guidance. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)
De Smet et al., Journal of Controlled Release, submitted for publication (2010).

Carrier-based drug targeting approaches to deliver the bioactive molecule at the target site have been under investigation for at least three decades. Liposomes, polymeric nanoparticles and micelles are the systems of choice. For targeting to tumour and inflammation sites, two approaches have been tried, either alone or in combination. (1) As the blood wall endothelium at such pathological sites is more permeable than endothelium elsewhere in the body, nanometer sized particles have an escaping tendency at the diseased site (the so-called Enhanced Permeability and Retention effect (EPR effect)). (2) The second, alternative approach is to attach to the carrier system ligands to target specific molecules (over)expressed at the diseased site) for preferred docking at the pathological site. This approach can only work if the carrier system can access the target cells, e.g. if the target cells are circulating in the blood or when the system can escape from the circulation into the target site upon intravenous injection. So far, at most 5–10% of the drug load reaches the target site (tumour, infection site) upon intravenous injection of such (targeted) carrier systems. That means that 90–95% ends up elsewhere in the body with a chance of inducing side effects. This off-target uptake is particularly important when the (targeted) carrier system with a cytotoxic pay load accumulates in certain organs/tissues such as Kupffer cells in the liver and macrophages in the spleen. These are the 'natural' off-target sites where nanometer-range carrier systems such as first generation liposomes and nanospheres end up. This observation calls for bioactive molecules that have low off-target pharmacological activity. Target site specific triggered release of the bioactive from the carrier system, as discussed below, may help to reduce off-target accumulation of the bioactive.

Here we will further focus on an integrated approach where non-invasive imaging techniques, smart drug delivery systems and non-invasive triggering technologies are combined to treat individual patients: Magnetic Resonance Imaging guided High Intensity Focused Ultrasonic (MRIgHIFU) radiation of a primary tumour or metastases where drug deposition is only locally initiated. A typical set up is the following (cf. Fig. 3): (1) MRI is being used to image the site(s) (e.g. tumour, metastases) where delivery of a bioactive is required. (2) The bioactive (typically the cytostatic doxorubicin) is encapsulated in (PEGylated) liposomes with prolonged circulation times. The liposomal bilayer is chosen such that fast release occurs at temperatures a few degrees above body temperature (e.g. ThermoDox, Celsion Ltd.) (De Smet et al., 2010). Upon intravenous injection these nanometer-sized liposomes have a tendency to localize in tumours because of the relatively open structure of the vasculature in fast growing tumour tissue (EPR). (3) A field of high intensity ultrasound radiation (HIFU) is generated with the MRI identified target tissue as the focal point of radiation. This locally induces a temperature increase of a few degrees, triggering local drug release. Temperature increase can be mapped again by MRI (Böhmer et al., 2009). The co-encapsulation of a MRI contrast agent (Gadolinium, Gd) allows monitoring the increase in liposome bilayer permeability during the mild heating process by measuring Gd signal changes (De Smet et al., 2010). Langereis and co-workers used 'chemical exchange saturation transfer' (CEST) principles to monitor the drug permeability of the nanomedicine system (Langereis et al., 2009).

Variations on this 'MRIgHIFU-drug loaded liposomes' scheme are studied as well (Deckers et al., 2008; Böhmer et al., 2009), e.g., a different approach was described by Rapoport et al. (2007). In their study ultrasound was used both for imaging and for triggering doxorubicin release from polymeric micelles at the target site. Another example is described by Ponce et al. (2007) who used an intratumorally located heated catheter to trigger and monitor release of doxorubicin (Dox) and manganese (Mn), respectively, from Dox/Mn-containing liposomes in tumour-bearing rats. The manuscripts referred to are from the last three years. It is clear that these spatial and temporal controlled

delivery techniques are still in their infancy, but have great potential.

2.1. Concluding remarks

In this Commentary we addressed the point that one needs new, integrated forms of medical intervention to realize personalized treatment approaches. The example of MRIgHIFU clearly shows that for optimizing treatment against cancer or serious infectious diseases, one should 'look over the fence' and combine different technologies such as image guidance for radiation treatment and the triggering of smart nanotechnological systems for temporal and spatial delivery of the bioactive. Much has been achieved in the last years, but the critical importance of multidisciplinary input should be reiterated wherever and whenever possible.

When we look at our wish list for optimization of therapy of serious diseases such as cancer, then enhanced resolution and target site recognition of the imaging techniques are high on this list. Resolution of MRI and CT may be <0.5 mm metastases still need to be >0.5 cm to be identified. As early stage identification of metastases improves the success rate of cancer therapy, it would certainly help to bring this lower limit size limit down. Another point on the wish list is to choose rationally (or design) new bioactive molecules specifically designed for the job. For example, even when successful targeting has been achieved, the major part of doxorubicin in nanoparticles ends up outside the tumour in macrophages in liver and spleen. These organs are therefore at risk to suffer serious side effects. Can't we think of (new) bioactives that lose their potency over time after injection and while being located inside the carrier? When intact nanoparticles 'overshoot' the target site and end up elsewhere, a chemically labile bioactive will lose its pharmacological effect in the nanoparticle and so reduce side effects upon its slow release.

Finally, the fast integration of imaging and drug delivery technology poses new challenges to the (industrial) scientific world and even more so to the regulatory bodies involved in the approval processes of these new approaches: different scientific disciplines with different cultures meet. The EMA and the FDA both recognize this and started their working groups and consultation rounds to decide what regulatory scheme will successfully guide these new, integrated therapeutic protocols through the approval process.

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