

## ***Personalised cancer treatment – Fad or future?***

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***Introduction: Oncology spearheads the push towards personalised medicine.***

There can be no doubt that the advent of the human genome and the subsequent development of genomics, kinomics, pharmacogenetics and proteomics is pushing medicine towards an individualised approach and that oncology is at the forefront of that movement.<sup>1</sup> However, despite the optimism, the huge explosion in research has yet to amount to any substantial clinical benefits<sup>2,3,4,5</sup>, outside of a few novel (albeit successful) treatments (ie imatinib, trastuzumab)<sup>6</sup>. The challenges facing personalisation of treatment are substantial, and include everything from the heterogeneity of cancer<sup>7</sup>, reproducibility of microarray results<sup>8</sup>, complexity of cancer cell signalling pathways<sup>9</sup> and economic considerations<sup>1</sup>. Despite the difficulty facing the trend towards personalised medicine, dismissing it as a simple fad would be to completely and ignorantly ignore the vast potential it has, even if the promises it holds may take some time to be realised.

***History: Moving into the second golden era of cancer treatment.***

Whilst it had been known during the 20<sup>th</sup> century that cancer was a genetic disease of the cell, the first landmark paper that demonstrated that cancer development was due to more than one gene mutation was published a mere 25 or so years ago<sup>6</sup>. Building on that knowledge, and with the advent of the human genome project, the number of genes identified in the development of cancer is now substantial, currently pegged at around 291<sup>9</sup> as is the potential therapeutic targets with an estimated 2-3,000 genes encoding “druggable” G-proteins, ion-channels or protein kinases<sup>10</sup>. This new knowledge has effectively signalled the end of the “first golden era” of cancer treatment, which started in the 1940s with the discovery of the effectiveness of the alkylating agent nitrogen mustard against non-Hodgkin’s lymphoma<sup>9</sup>.

Despite the success of generalised cytotoxic agents, their clinical usefulness is limited by their often debilitating side effects, low specificity<sup>11</sup>, low concentration being delivered to tumours (studies have shown that the concentration of doxorubicin in Kaposi’s sarcoma may be as low as 0.001%)<sup>12</sup> and the development of resistance, an almost universal feature of cancer cells<sup>9,13</sup>. Although the success of the first generation of targeted drugs (imatinib, trastuzumab)<sup>6</sup> cannot be denied despite initial concerns, (even though as little as 10 years ago the approach to small molecule inhibition of kinases was seen as a very high risk venture<sup>9</sup>), the transition from generalised cytotoxic therapy to targeted, individual therapy is a vast gulf that will take some time to cross. It’s worth remembering that the development of a drug by the pharmaceutical industry is easily in excess of US \$800 million, and only 5% are clinically viable<sup>9</sup>, thus talk of targeting specific proteins is still very much a long term goal.

***Microarrays: Genomics and the unravelling of the cancer genome.***

Cancer is a genetic disease<sup>2</sup> and as such understanding its biology is critical to fully mastering our control of it. However, with microarrays making it possible to visualise the gene expressivity of thousands of genes at once as opposed to one with more traditional methods, our level of understanding of the complexity of cancer genetically has in itself imposed new challenges<sup>7</sup>. It is now known that cancer varies genetically and phenotypically between patients with identical stages and

types of cancer<sup>14</sup> but even from cell to cell, with leukaemia cells showing marked difference in protein phosphorylation between individual cells<sup>15</sup>. Further confounding this, studies are increasingly showing that most of this gene transcription is necessary to simply keep the cell functioning, and that it is only a small percentage of differences in protein transcription that differentiates it<sup>15</sup>. Other complicating factors include events such as alternative RNA splicing, which leads to different protein products which isn't able to be appreciated by microarray analysis, epigenetic changes such as DNA methylation<sup>14</sup> and differing activity levels of protein products<sup>15</sup>. Microarrays have been quite useful in cancer subtype classification, (ie in classifying breast cancer into 5 subtypes)<sup>10,13</sup>, elucidation of cancer promoting genes<sup>9</sup> and the discovery that the ability to metastasize (long believed to be a late development in the relentless advance of cancer) is now encoded relatively early on in tumour growth<sup>7,16</sup>.

Microarrays show considerable potential in being able recognise disease susceptibility genes, potential therapeutic targets and expression profiles in response to chemotherapeutic agents which may help overcome drug resistance or show sensitivity<sup>7</sup>. The technology is still limited though, despite our advances in genetics there are abundant examples of how cancer cells evade our therapies in which we have no real understanding of the underlying mechanisms. Examples include a mere 10% response rate to cetuximab in colo-rectal cancer<sup>17</sup> with no real understanding of the underlying mechanism involved, and increased expression of MDR in breast cancer cells (52% post-treatment, 41% pre-treatment)<sup>13</sup>. Although much of this can be put down to cancer having a strong selection pressure to survive<sup>6</sup>, the discovery of exactly how cancer potentiates these ability remains to be established, and thus little clinical utility has come out of such research.

Microarray technology is not without its criticisms. Studies have critiqued microarray data for having little standardisation in methods, data analysis and differing arrays being used<sup>7</sup>. Some microarray studies have not predicted patients response to treatment any better than by random chance alone<sup>14</sup>, small sample size<sup>18</sup> and the biological variability between patient samples as well as the huge variety of biomarkers to be measured imposes significant challenges on microarray technology<sup>3</sup>. In addition, cancer cells change gene expression when removed from their environment, potentially giving misleading results<sup>14</sup>. The reproduction and validity of microarrays for tumour markers needs to be addressed carefully<sup>3</sup>, as is the concern that any test which screens for a particular number of genes may miss critical genes<sup>6</sup>. Conversely to this, even mathematically simple assays are a vast improvement over clinical tools available now<sup>6</sup>, and at the time of publication two assays were already commercially available, one measuring 70 genes and the other 21 for breast cancer patients<sup>1</sup> which indicates great hope in this field.

### ***Proteomics: The other side of the genomic equation.***

Whilst microarray and genomic technology might be able to identify target genes and help prioritize potential lead compounds<sup>10</sup>, without knowledge of the proteins those genes produce half of the equation to understanding cancer biology is missing. Proteomic arrays can be used to identify the amount of phosphorylated proteins within a cell and monitor the information flow within a cells network, which when coupled to changes in microarray gene expression for cancer cells provides vast amounts of information about the functional state of cancer cells<sup>14</sup>. Curiously, despite the complexity of cell signalling pathways, cancers have been hypothesised to display "oncogene addiction", in which there is selection for a critical oncogenic signalling pathway (as opposed to the multiple pathways cells normally employ) which, if identified, provides a very enticing target for targeted therapy<sup>10</sup>. With the pharmaceutical industry now moving more towards rational drug design, understanding the molecular basis of cancer gives us a huge platform in which to launch the next generation of targeted drugs<sup>9</sup>. Mapping entire networks, rather than individual biomarkers, is acknowledged as the key to this personalised treatment development<sup>3</sup>.

Of key note in potential targets the protein kinase family. Of the roughly 291 oncogenes thus identified, 27 (or 6%) are protein kinases, which is a vast over-representation<sup>9</sup>. The success of imatinib has already shown this class is readily druggable, and provides an enticing target for future rational drug development<sup>9</sup>. Ultimately, with the signalling pathways mapped out in the future, the hope would be to employ several inhibitors against the one pathway, at much lower concentrations than traditional chemotherapy. As each step in a signalling pathway is affected, the concentration of drug needed at the subsequent step is lower, which has huge implications for safety and efficacy of treatment<sup>7</sup>.

Despite these bold claims, proteomics is also very much in its infancy. Despite increasing knowledge of phosphorylation patterns in cancer cells, activators of phosphatases are not yet available<sup>9</sup>, and that despite the amount of data in this area the clinical success has been very limited, with astounding successes like trastuzumab likely to be the exception rather than the rule<sup>5</sup>. Other limitations include the challenge that proteomics requires more material than the small amounts provided from patients for analysis, and all the proteins studied are in a denatured form which often doesn't adequately depict the state of the cell circuitry material<sup>7</sup>. There are current problems with assay development, traditional methods such as ELISA are much too expensive to implement on a large scale<sup>3</sup>. Thus, even though proteomics has made huge promises, it shall be some time before we realise them in clinical practice.

#### ***The Others: Other clinical options for targeted therapy.***

Nanoparticles are starting to have considerable interest shown in them, not only as a means of delivery of drug to cancer cells, but also in imaging<sup>7</sup>. Already liposomes have been used to exploit the over-expression of fenestrations in cancer vasculature in breast and ovarian cancer<sup>4</sup>, and many more particles are in development. Nanoparticles can be divided into two main classes, those with organic molecules as a major core material (ie carbon nanotubes) and those with metals<sup>19</sup>. Nanoparticles employ targeting molecules on their outer shells such as antibodies or RNA aptamers in order to help them reach their target, delivering drugs in a much higher concentration than is possible for current cytotoxic therapy<sup>4</sup>. Targeted antibodies have been reported to reach tumour cells in a 1-10,000 rate, a significant improvement on the 1-100,000 seen with conventional therapy<sup>12</sup>.

Whilst many nanoparticles are currently under investigation to deliver drugs to target tissues, others are being looked at for heat ablation. Dielectric core nanoparticles, which emit near infrared light, are able to convert light into thermal energy, producing local tumour ablation without damage to surrounding tissue<sup>19</sup>. These ablation methods can produce temperatures of over 50°C in tumour tissue yet not in surrounding ones, and offer great hope in the future of targeted therapy<sup>12,4</sup>. Other potential uses include that in imaging, with magnetic nanoparticles able to be used in conjunction with an MRI, quantum dots being induced to fluoresce without loss of light intensity (photobleaching), or directly delivering contrast to tumour cells<sup>19</sup>.

Another novel approach involves the use of embryonic stem cells. Lacking HLA antigens, they avoid immune reactions against them and have been shown in studies to actively seek out glioma cancer cells within brain tissue<sup>20</sup>. In fact, the very presence of stem cells appears to have anti-tumour effects due to an unknown phenomenon<sup>20</sup>. They have also been modified to constitutively express IL-4 which has been shown to improve survival time in mice, but is a technology which is even more infant than any of the others previously discussed<sup>20</sup>.

Nanoparticles are of course not without their faults. There are grave concerns on toxicity, particularly in those which use metals as a core<sup>19</sup>. In addition, they are expensive to produce, and,

with the exception of heat ablation, are mainly being used to deliver the same chemotherapeutic drugs which personalised therapy is trying to move away from<sup>20</sup>. Thus they are best seen as an adjunct to the emerging fields of proteomics and genomics, with the data gained from those complementing the design of new nanoparticles and providing them with new targets within the cancer cell. Another criticism, particularly one in the light of the topic of this essay, is that they aren't really a *personalised* treatment per se, at least not in the same way as genomics and proteomics is promising, more a better way to deliver drugs than the generalised way which currently exists. Thus, the author can't endorse them in the same way as individual gene mapping for patients as is being promised with other personalised technologies.

### ***Economics: And other challenges on the road ahead.***

Concurrently with the development of genomics to map the genetics of cancer, pharmacogenetics is becoming its own field of research which promises to individualise and improve patient care. However, just like the initial hype with microarrays has been dulled somewhat by the complexity of the genomes they revealed<sup>2</sup>, pharmacogenetics seems to have somewhat exaggerated claims, with a MEDLINE search revealing only 11% of articles featuring primary research<sup>21</sup>. Although it has been widely stated that personalised treatment will lead to considerable economic benefit through reduction of side effects and costs<sup>10,17</sup>, other authors take a more critical view. Pharmacogenetic advances would be rendered uneconomical if patients who were predicted to have a poor outcome were to take the drug anyway, and with cancer being such a challenging and devastating diagnosis hope, even in the face of being told otherwise, plays an important role in patients decision making<sup>21</sup>. Further compounding this is the consideration that governments mightn't be willing to subsidise drugs for patients if it had been shown that they were likely to have little effect, which produces major economic headaches as well as ethical questions<sup>21</sup>.

Also drastically needed are novel biomarkers to help detect cancer before it reaches the symptomatic, bulky tumour stage<sup>2</sup>. In this area, personalised treatment has been somewhat lacking. Despite the realisation that DNA in plasma tends to be higher in cancer patients, cancer cells are still hard to elucidate from a patient's blood<sup>14</sup>. In addition, methods to predict an individual's response to therapy is still largely unavailable<sup>16</sup>, and current prognostic factors are inappropriate and of little use for tailoring individual treatment<sup>2</sup>. Another consideration is that genetic risk information is only useful in preventing disease if there is able to be behavioural or medical interventions<sup>22</sup>, and prognostic data from microarrays is only useful if alternative treatment exists<sup>18</sup>, which for most current cancers and cytotoxic chemotherapy is not a reality. The progression of understanding of cancer biology has not translated into clinical success<sup>4</sup>, thus the author advises caution and restraint when dealing with these topics, as the promises and knowledge gleaned has not yet been applicable clinically, and as exciting as these developments are, traditional chemo and radiotherapy is still the mainstay of practice and will be for some time.

### ***And finally...***

An interesting point was made in the *Journal of the American Medical Association*. Their stance was that "personalised medicine" was merely a buzzword for individual drug regimes, and that true personalised medicine has in fact been practiced for centuries by physicians attending to their patients by their bedside rather than any new technology<sup>22</sup>. The author believes this stance is a very wise one to take, for knowledge of a patients genome is still no match for sympathy, empathy and understanding of the patients individual situation. Although the future is very exciting in

technological terms, we must ensure not to lose our human compassion and understanding for each patient, as they are more than a sequence of base-pairs, and always will be<sup>22</sup>.

***Conclusion: The future is bright, but the present is reality.***

There can be no question now that individualised treatment is the future of oncology. The promises being made are amazing indeed, but the lack of clinical success so far must always be remembered before charging forward and making unrealistic expectations of a technology very much in its infancy. It's been a mere 10 years since the human genome was sequenced, any clinician who thinks the era of personalised medicine is now is nobody's fool but their own. This essay asked if personalised cancer treatment was a fad or the future, and the author must conclude it is indeed the future. However, treating that future as if we could use it today is nonsensical, and the gulf we must cross to get to that stage is vast. But not insurmountable.

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