Angelo Di Leo:

mapping the geography of breast cancer

Marc Beishon

Angelo Di Leo cut his research teeth on early studies into personalising chemotherapy. Mapping the geography of interconnected biomarkers that can predict which breast cancer patients respond to what is not a guiding principle for Di Leo so much as an immediate task – a task that he feels would progress far faster were less effort wasted on trials that fail to address differences in tumour biology.

The hottest topic in cancer has for some time been personalising treatment for patients, and interest continues to be fuelled by the explosion in new biological data now feeding into thousands of research programmes around the world. Breast cancer has long led this field, and many experts are predicting major breakthroughs in treatment planning thanks to technologies such as genomic profiling.

But as *Cancer World* has often reported, the complexity of this genetic information alone is enormous. And what we are learning now about the structure and subtypes of tumours is adding yet more layers of complexity says Angelo Di Leo, one of the new wave of top breast cancer clinicians.

"We have of course known for some time that one patient may have a different type of breast cancer from another, but we are now finding that a tumour in one person has different parts that do not play the same role in the life of the cancer. We also know that parts of tumours interact with the host in different ways and can also change over time according to the treatments we give. It's an extraordinarily complex system."

Di Leo, who chairs the oncology department at Prato Hospital in Tuscany, Italy, is a medical oncologist who worked on the first efforts to personalise cytotoxic chemotherapy treatment in the late 1990s, and is now one of the leading international authorities on where the most promising avenues lie, and he is optimistic. "Despite the complexity, I do not believe we have reached a plateau in progress with breast cancer, and with other tumours for that matter," he says. "The biological information will allow us to make substantial improvements in targeting."

He and his team are involved in much of the cutting-edge research into breast cancer, not only studying the latest targeted biological agents, but exploring fields that could help better target these new therapies, such as metabolomics, the study of compounds arising from metabolism, which could give rise to new biomarkers for cancer types. But Di Leo has largely made his name in the field of targeted chemotherapy – finding out which patients benefit most from many existing cytotoxic drugs –

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and he considers we are in a position to uncover much more information about where they can best be applied, alone or in combination with newer technologies, including by going back to data from hundreds of thousands of women who participated in trials that did not – or could not – take into account the biological information we have now.

What is helping Di Leo make his case is having his own oncology unit that he started from scratch in 2003. Up until then, Prato – a city often bypassed in favour of the more glamorous, nearby Florence – had little integrated cancer care to offer patients. After working in Belgium for a long spell, Di Leo took an opportunity to build a new research-oriented oncology department on his return to Italy, rather than take a number two position in a larger, established centre. "The Italian Association for Cancer Research (AIRC), the major funding agency in Italy supporting investigator-driven research, played a critical role in facilitating my programme in Prato. I am also thankful to the Sandro Pitigliani Foundation, which has supported this project since September 2003 even though we were at the beginning of this new venture in Prato."

Given a budget to set up his own vision of an oncology department – and despite inevitable Italian bureaucracy – Prato now has multidisciplinary teams for several cancer types, and a particular strength in breast cancer, as well as a translational research lab. It is also part of a growing regional network – the Tuscan Cancer Institute (Istituto Toscano Tumori). None of this existed a few years ago and it is now a platform for not only enhancing patient care but also developing the careers of young oncologists (Di Leo also has a teaching position at Florence University), and has put Prato on the oncology research map. Oncologists at the Sandro Pitigliani medical oncology unit, Di Leo's key creation, are now regular contributors to major journals and make presentations at top conferences.

"Personalisation is also about taking into account the health and preferences of a patient"

Enthusiasm and experience. Di Leo is very proud of the team he has built up in Prato, and has high hopes of attracting back some of Italy's brightest and best who are currently working abroad

Di Leo confesses to great pride in the team he heads. "It is a perfect example of integration between senior and junior people, who bring either experience or enthusiasm to our programmes. Together with my colleague Augusto Giannini (head of pathology) we are now trying to facilitate the 'return' of bright Italian scientists who have been working abroad for some years." Libero Santarpia, a young pathologist with expertise in genomics, is one such returnee, who recently joined Di Leo's team as leader of the translational research unit, after spending five years at the MD Anderson Cancer Center.

But personalisation is about much more than just the biological behaviour of a tumour – it's also about taking into account the health and preferences of a patient, as Di Leo stresses. "People come up to me in conferences and ask, 'What is the first-line treatment for metastatic breast cancer?' I say, 'I don't know – it depends on the patient in front of you.' You can't possibly map out an algorithm for late-stage disease as there are so many variables, such as the patient's preferences for the level of aggressiveness of treatment, how and when drugs are taken, whether they can tolerate hair loss and other side-effects, and so on. You might just be able to do it for early-stage cancer but for metastatic disease it's impossible."

And communication with patients – especially the first appointment, where impressions are made – can be critical in determining the success of treatment, adds Di Leo, who holds strong views about the quality of doctor–patient interactions. His own career path, he says, has been very helpful in learning the

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craft of the medical oncologist from this standpoint and other aspects of basic clinical work, as well as the research which he subsequently became heavily involved with.

He had the usual motivation for wanting to enter medicine – a desire to help people. "But I was also fascinated by the biological aspects, the complex mechanisms that regulate the body. Oncology is a natural choice for combining these interests." After completing a degree in medicine and surgery at the University of Palermo, he went to work at the National Cancer Institute in Milan in 1989, while also gaining a postgraduate diploma in medical oncology at the University of Pavia.

"My first priority in Milan was to understand how to be a good medical oncologist and provide a good level of care to cancer patients with all tumour types – you can be the brightest clinician around but you have to learn how to communicate with patients. I think also that it is mistake to specialise too early in your career – it's much better to cover different areas of medical oncology and develop a transferable platform – a methodology you can apply to any setting."

Di Leo is concerned too, like many medical oncologists, about the lack of standardisation of training and practice for the specialty around Europe. "Despite the efforts of ESMO [European Society for Medical Oncology] with its certification scheme, it's had little impact on the very mixed picture we see, such as clinical oncologists also carrying our radiotherapy in northern Europe, gynaecologists as breast cancer specialists in Germany and, until recently, in Italy you didn't even need any internal medicine training to become a medical oncologist.

"I've been involved also with the European Society of Breast Cancer Specialists [EUSOMA] on a survey of medical oncology training, which shows a pretty disastrous level of difference; we proposed a template of skills, but take up has been very poor."

Meanwhile in Milan it did not take long for Di Leo to become frustrated with patients' unmet needs, such as pain and lack of choice of drugs to control disease. "I started with prostate cancer, where the drugs we had were mostly not helpful for some patients because we had not yet made much progress in making the links between biology and the clinic, such as how to tackle hormone-refractory prostate cancer, which was the first trial I was involved with. The labs may have been making exciting discoveries but we were not translating them into clinical practice, so much of my research then was disappointing."

In Milan at that time Di Leo did not have the opportunity to step up to help close this major research gap, and he applied to several centres abroad, preferring to remain in Europe rather than go to the US, where he had already completed two short spells as a visiting physician. He succeeded in landing a full-time post in the chemotherapy unit at the Jules Bordet Institute in Brussels. "The institute certainly wasn't the force it is now back in 1996," he says, "but Martine Piccart was there and just starting on her major work in breast cancer, and as soon as I met her, any doubt I had disappeared."

Piccart-Gebhart, as she is now, had just started the Breast International Group (BIG), and she immediately pitched Di Leo into international collaborative research and also supplied that vital lab-clinic interaction he'd been missing in Milan. "I found that research doesn't have any borders and that you can collaborate with the best people by finding who is working on complementary aspects of a problem elsewhere. It opened a new world to me."

Di Leo was given one of the first personalisation research projects in breast cancer, comparing an anthracycline drug with the CMF regime in early-stage disease to see who would benefit most from which treatment. "We collected tissue from centres around Belgium, which was successful as it is not a large country and people were very helpful, and we focused on the topoisomerase II alpha [topoIIα] marker, finding also a group in Finland that was expert in the lab work, while we had the clinical side. We invited them to a seminar in Brussels – I remember how excited everyone was that an enzyme in the nucleus of a cancer cell could be helpful at predicting the outcome of a treatment.

"The hypothesis was that the amplification of the topoIIα gene was associated with the activity of the anthracycline drug – if there was protein overexpression then the drug would hit its target and be particularly effective, and our results were positive and confirmed by other groups. But when I look back on our 2002 paper, I now see that the problem turned out to be more complex, and this has not led to a conclusive change in practice – it needs to be combined with other biological information. But what it did lead to was a new field of research, which is targeted chemotherapy." The search is on now for more

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biomarkers that could potentially be helpful in selecting tumours that are particularly sensitive to DNA damaging cytotoxics.

Di Leo went on to run one of the first BIG trials, on the taxane docetaxel, and its role in breast cancer, identifying centres worldwide and recruiting people to conduct the research. "I also helped set up a translational research unit with pathologist Denis Larsimont, to go back to the tumours and see what benefit we were gaining – it was what I wanted to do in Milan but only achieved it in Brussels. Martine Piccart helped drive funding for the lab, and it grew rapidly, and it was hard to leave it when I came to Prato. But it's been a model for what I've gone on to do here."

Following his move to Prato in 2003, Di Leo has considerably upped his involvement in international research and conferences, finding himself much in demand as he continues to research the targeting and optimal use of systemic therapies, together with his team and colleagues abroad. They are also pursuing more fundamental laboratory science such as studying the characteristics of circulating tumour cells.

Di Leo recently presented research about optimal dosages for fulvestrant. "The hormonal therapy agents are for the 60%–65% of women with endocrine disease, but within this group there are half who are very sensitive and half less so. Most don't need chemotherapy and it has been the first generation of genomic signatures that has helped consolidate this concept."

The MINDACT trial, the large project that is using a genomic signature that could better determine which women can avoid chemotherapy, is a good study, he comments. "It's logistically complex but has been the first attempt to test such personalisation on a large scale – other trials are mainly retrospective and of moderate size. It's not going to provide all the answers but there have been some big surprises – the signature has shown the exact opposite in some cases of what you would expect when you were convinced to give or not give chemotherapy based on traditional markers, and the grey area we are considering here is not small – it is 25%–30% of the endocrine-sensitive population."

New chemotherapy agents, he adds, are also now available that are helping to improve quality of life, for instance because they can be taken orally. "You can see how it lifts women's spirits when you offer them less intensive treatment," he says.

Then there are of course the targeted biological therapies. "While some have clearly changed the story of a disease – trastuzumab and lapatinib for HER2-positive breast cancer, and imatinib for CML and GIST – the new wave of drugs has not given us what we expected. I'm not saying they are not good – they work, but the benefit is not great and some are associated with relevant side-effects. What we need to do is carry out much more work on trials on who will derive the most benefit from these drugs and stop trialling targeted treatments on untargeted populations." The classic examples, he notes, are the anti-EGFR therapies, which were only marginally useful in tumours such as lung overall, but have since been found to be active in certain groups.

But faced with the Catch 22 of not knowing whom to target until the expensive large trials have been done, Di Leo reckons that much gain could be made by much closer interaction with laboratory scientists. "The problem is clinicians and pharmaceutical companies don't talk to them enough – for example, with agents such as the anti-angiogenic

"We need to stop trialling targeted treatments on untargeted populations"

A constructive partnership. Di Leo's wife, Laura Biganzoli, is a medical oncologist running the geriatric oncology programme at the same hospital

drugs, the lesson they have given us is to use lower doses continually. Instead we were giving higher dosages for a shorter time."

He also reckons that the new levels of complexity under investigation about intra-patient heterogeneity – that is, variation in a tumour within an individual – will provide vital clues to progressing the targeting story. Following the classification of breast cancer into its main molecular types – luminal A and B, HER2 and basal (triple node negative) – the next steps are to look at how the different types of cell that make up these tumours behave and interact with the host, among other factors.

Not all cancers of the HER2 type, for instance, behave in the same way, he points out, and there is crossover between the groups; the second generation of genomic signatures is attempting to provide information across the subgroups. "Evidence is emerging that exciting new agents such as the PARP inhibitors – which could be most active in the hard-to-treat triple-node-negative cancers that often affect younger women – might also be active in other subtypes of breast cancer." The PARP inhibitors – which indeed have generated much interest in the cancer community – could be teamed with cytotoxic drugs to make a double attack on the DNA repair mechanisms in tumours, he adds.

With some parts of a tumour interacting with the host in different ways, or an agent suppressing one region and not another, and the heterogeneity among the first level of subtypes, Di Leo says what we need is a 'geography' of each breast cancer. Much of the latest thinking was discussed at IMPAKT, a European translational research meeting in Brussels in May, that Di Leo co-chaired with Christos Sotiriou (a former colleague at the Jules Bordet), and which is now in its second year. "It fills one of the main gaps in European breast cancer meetings, although I would still like to see more smaller events for young investigators and clinicians." (Webcasts of IMPAKT talks can be replayed at esmo.onsite.tv/impakt2010, including one on metabolomics by Catherine Oakman, an Australian oncologist working at Prato and one of Di Leo's current key co-authors. The metabolomics work is being done in conjunction with the Memorial Sloan-Kettering Cancer Center in New York.)

"Given the biological heterogeneity within the same tumour, we may need a 'map' of each breast cancer"

Another important part of the picture he mentions is molecular imaging. "With the new tracers we have now we can see the tumour's metabolic activity, and if it's dying, growing or invading. For example, BIG is looking to start a neoadjuvant study using latest imaging techniques for an important target for oestrogen-positive tumours."

Meanwhile, in the clinics at Prato, the number of new cancer cases seen has shot up to 1500 a year and Di Leo's team is monitoring some 20,000 patients within the regional network structure. "Italy has decided to invest in regional development, and each region is reorganising its health services to provide better care and prevent patients moving between areas, which would reflect badly on our care and also be a loss of funds," he says. Competing to offer the best care can only be good, he adds, so long as protection is provided for regions in the south of Italy that historically have been less competitive.

Just as a cancer treatment decision is often the only opportunity, so too is the first meeting with a cancer patient. "We schedule at least 45 minutes for a first consultation – if a patient feels they are welcome and their problem is well understood, they are much more likely to trust us if we need to help them with more bad news, or if we need to change their treatment.

"What we also do – which is also very demanding in time – is have a day each week when patients and their families can come in and talk to us about their situation, and where we do not schedule any clinical activities. We discuss concerns about treatment, clarify issues and get feedback about how we are doing, which we also do with questionnaires. You can get so wrapped up in treatment plans that you may not discover, as we did, that actually some patients are most concerned about not being able to park by the clinic when they came for chemotherapy."

For their part, he promotes among his clinicians not only good communications but also consistent practice according to guidelines. As he notes, with many expensive drugs at their disposal, the only way to control costs at local level is to give them correctly – not over- or underused. "We have weekly meetings where we discuss who should have treatments and who should not. I'm trying to keep a high level of consistency – it would not be good if one oncologist was denying a drug but next door another was giving it to the same patient."

Among his many activities Di Leo sits on the St Gallen panel – the treatment consensus conference on breast cancer held every two years in Switzerland – but he warns about the use of guidance and tools that do not provide an indication of individual benefit. He has a particular concern about oncologists who rely overly on Adjuvant! Online, the web-based resource. "It's easy to use and you get nice graphs of risks and benefit but it can mislead about the

SAY GOODBYE TO UNTARGETED TRIALS

The hugely complex nature of breast cancers – their heterogeneity – poses major challenges for oncologists making decisions about chemotherapy because the results from trials are often hard to tailor for an individual patient. As Di Leo and colleagues explore in a review paper, 'Adjuvant chemotherapy – the dark side of clinical trials. Have we learnt more?' (*The Breast* 18 S3), there is heterogeneity not only in the biology of breast cancers, but also in treatments according to dose and scheduling, in mechanism of action (some drugs have non-cytotoxic benefits, for example), and in risk – some women do well even without adjuvant treatment that many would have given.

The paper gives a good overview of progress and promise in establishing markers to unpick some of this variation and target cytotoxic treatments better. And the message is clear – this is not the future but should be the focus of current work. A recent editorial written by Di Leo and Oakman titled 'Ode to a past emperor' (*JCO* 28:18) is a devastating critique of a cytotoxic chemotherapy trial reported in the same issue where they take apart its claim for significance, pointing to poor design and missed opportunities to investigate beyond the 'one size fits all' mentality. As they say, "Whereas the old generation of clinical trials has been pivotal in shaping our adjuvant chemotherapy approach, the rule of the old empire has come to a close… Patient eligibility was defined by tumor risk factors. Future generations of trials must abandon this method of patient selection and define eligibility by tumor biology… The era of breast cancer as a homogenous disease is no more."

benefits of hormonal and chemotherapy as it assumes all patients derive equal benefit. It should not be used for treatment decisions, but it can be useful for estimating prognosis, say the 10-year risk of death of someone with a small, node-negative, endocrine-resistant tumour."

Along with BIG, other major groups that Di Leo and Prato work with include the International Breast Cancer Study Group (IBCSG), and the Oxford-based Early Breast Cancer Trialists' Collaborative Group, which crunches data from trials worldwide to understand better what is happening with systemic therapies. Major problems persist, however, in the design and aim of many trials, he says. "We are in a changing phase. Typical examples are the taxane trials of the last decade, some of which have not yet reported. We have some 60,000 patients in these trials – far too many and we are duplicating effort in too many studies. In some cases investigators prefer to be leaders of a small trial – we simply do not need 25 or more trials to demonstrate the effectiveness of taxanes. What's more, many of these trials cover all patient types but on their own are not big enough to reveal any significant data about subgroups."

Di Leo has also been one of the few Europeans on an important committee at the American Society of Clinical Oncology (ASCO). "This was on grant selection for young investigators. I'm very keen to promote younger people and I send them to conferences where I can, although the organisers obviously want the senior people to come. I also give them first authorship on papers. I think if you are working at a centre where you cannot research a new drug or marker, you can instead discover promising young people as an equally important contribution." As Di Leo himself is only 46, this is a mark of his own considerable achievement in the first half of his career.

Di Leo is now on the scientific advisory boards of Susan G Komen for the Cure and the Breast Cancer Research Foundation, both of which allocate many millions of dollars of research funds a year, with Prato among the beneficiaries. Di Leo recognises that sometimes advocacy groups do not push in a logical scientific direction. "But overall the balance is positive – before these groups came along many issues simply were not in the minds of clinicians, such as all those personal variables for treating someone with advanced cancer. And they are on a learning curve too – for example, when I gave a talk to a Europa Donna meeting at the European Breast Cancer Conference in Barcelona on targeted chemotherapy, I found they had a level of caution that was not apparent 10 years ago."

One major factor in his life that spans both home and work is his wife, Laura Biganzoli, who is a medical oncology specialist based in his own department, and whom he met in Milan. "Yes, I'm nominally her boss, but she runs her own programmes in the important and emerging field of geriatric oncology. The good side is that I have someone I can trust and talk to about work, but the bad side is you can talk too much about it back at home. But the key point for anyone who follows my type of career is to have an understanding and supportive family, especially given the travelling and late working I have to do." They have a daughter, Federica, who was born in Belgium – Di Leo keeps telling her she's part of the new Euro generation when she's teased at school about not being a proper Italian.

Among his key mentors and colleagues are of course Martine Piccart-Gebhart, and also Aron Goldhirsch at the European Institute of Oncology in Milan, who pioneered understanding of the complex biology behind endocrine treatment in breast cancer.

Plans for the next few years are clear. "I'm continuing to push the research on personalising chemotherapy – it will be part of our treatment options for a long time to come. I want also to accelerate and improve the efficiency of trials in BIG and IBCSG. And here in Prato I'll continue to improve care, ensure long-term commitment to oncology, and make us more visible in the wider cancer community, especially by promoting young people to take leadership positions in the clinic and lab."

Those who had not heard of Prato now have a new beacon to add to the cancer map.

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