

Hope on the Horizon

Towards new treatment
for breast cancer



DDResponse

The collaborative project DDResponse (2011-2015) is a consortium funded by the Seventh Framework Programme of the European Commission. It combines scientific, medical and pharmaceutical expertise from The Netherlands, Denmark and the United Kingdom. The aim is to make significant progress towards a more accurate prediction of individual responses to anti-cancer therapy and towards the development of new anti-cancer drugs.



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Introduction

Approximately 10% of all women will be diagnosed with breast cancer at some time. And even though treatment has improved a great deal in recent decades, the efficacy varies widely among patients. At the same time, every patient does suffer from the serious side effects of the anti-cancer treatment. How can this be changed?

By combining the expertise of laboratory scientists, oncologists and representatives from the pharmaceutical industry. These parties all have the same goal: improving treatment for breast cancer patients and diminishing the side effects. They know they can only achieve this goal through cooperation. The European DDResponse research project brings together researchers, oncologists and industrial partners in Denmark, The Netherlands and the United Kingdom. The project focuses on two major goals: better tailoring of the treatment to the needs of the individual patient, and the development of new drugs.

Personalised treatment

Despite the major improvements in anti-cancer therapy, many patients have to undergo several treatments to find out which one is the most effective. Better prediction of the patient's response to therapy would mean great progress, as it would reduce side effects caused by ineffective treatments. So the members of the DDResponse consortium search for characteristics that help in classifying the different types of breast cancer. This search is performed mainly by scientists in the academic centres, while the oncologists provide tumour tissue and the pharmaceutical companies supply the anti-cancer drugs. For some types of treatment a test to determine if a patient will benefit is well on its way.

New drugs

In addition to the currently available anti-cancer therapies, the quest continues to find new drugs that increase the effectiveness of treatment and/or diminish the side effects. Such new drugs would either be used alone or in combination with existing therapies. The pharmaceutical industry is leading in this part of the project. They have the tools and expertise to determine the possibilities of new drugs. On the other hand, academic scientists also define new options to improve drug efficacy and they provide invaluable basic knowledge on important biological processes. This helps in understanding why certain drugs are effective and others are not. Oncologists provide the tumour tissue and select patients for clinical trials. And in the end, they are the ones who will prescribe the new drugs as soon as they have been approved.

This brochure

In this brochure you will find background information on breast cancer, its link with DNA repair, the aim of the DDResponse project and the long scientific journey towards better treatment. Four years will probably not be enough to actually bring a new drug to the market, but a test to screen tumour tissue of individual patients for its response to therapy might be within reach. In any case, the consortium goes to great lengths to achieve major progress towards achieving its goal and there is certainly *Hope on the Horizon*.



Chapter 1. Selection for treatment

Don't let yourself be fooled by semantic inaccuracies. THE breast tumour does not exist. Neither does THE bowel tumour nor THE skin tumour. Each tumour is different, just as each patient is different. What does that mean for anti-cancer treatment?



It means that nowadays, we cannot predict accurately whether a treatment is going to work. Some tumours respond to the treatment, some don't. Medicine is therefore in urgent need of better tools to categorise patients based on the composition of their tumour. Increased knowledge and improved techniques may bring personalised medicine within reach, so every patient gets the treatment that works.

Better treatment

Some individuals have a higher chance of developing cancer than others. These people possess a so-called hereditary predisposition. There is no question that such a predisposition is an immense burden to the person harbouring it. On the other hand, knowledge of the mutation

underlying it can be very helpful for determining the proper treatment. If an oncologist knows that a breast tumour has a mutation in one of the Breast Cancer (BRCA) genes, he knows that the tumour cells lack an important DNA repair mechanism. Therefore, he knows that treatment through the inhibition of a second, complementary repair mechanism is an option - treatment that is more effective and reduces negative side-effects. Undoubtedly, there are other genetic defects in tumours that also have predictive value for the susceptibility to specific treatments.

Predicting response to treatment

How to identify these kinds of weak spots? Researchers currently analyse an extensive collection of breast tumour samples. They search for mutations in genes known to be involved in DNA repair. For mutations commonly found, whether they potentially predict a tumour's response to a certain treatment will be assessed. If so, biopsies (small pieces of the tumour) from breast cancer patients could be screened for that specific mutation, using it as a so-called biomarker. In a complementary approach biopsies are used to test different types of treatment outside the body, giving vital information to help predict treatment response.

Aim for the back-up plan

Concurrently with finding more genetic mutations predicting tumour response to treatment, scientists search for other clever ways to fight tumour cells. They have high hopes of finding more weak spots in tumour cells, in addition to the one described in this brochure (Chapter 3; Finding the weak spot). There must be more possibilities of finding treatment that takes advantage of the absence of a back-up DNA repair pathway. Cells have numerous back-up plans, which is one of the secrets of their success. It is therefore expected that other combinations of main parachute and safety parachute can be found for targeting by anti-cancer therapy.



Central role

Tumour's weak spots identified in this way might not only be of therapeutic relevance for breast cancer patients, but for other types of cancer as well. Defects in the repair of DNA damage are thought to be pivotal to the occur-

rence of all types of cancer. So analysing malignant material for the status of DNA repair will be very helpful in choosing the proper treatment for multiple tumour types. This research is therefore a hopeful and promising quest in our fight against cancer.

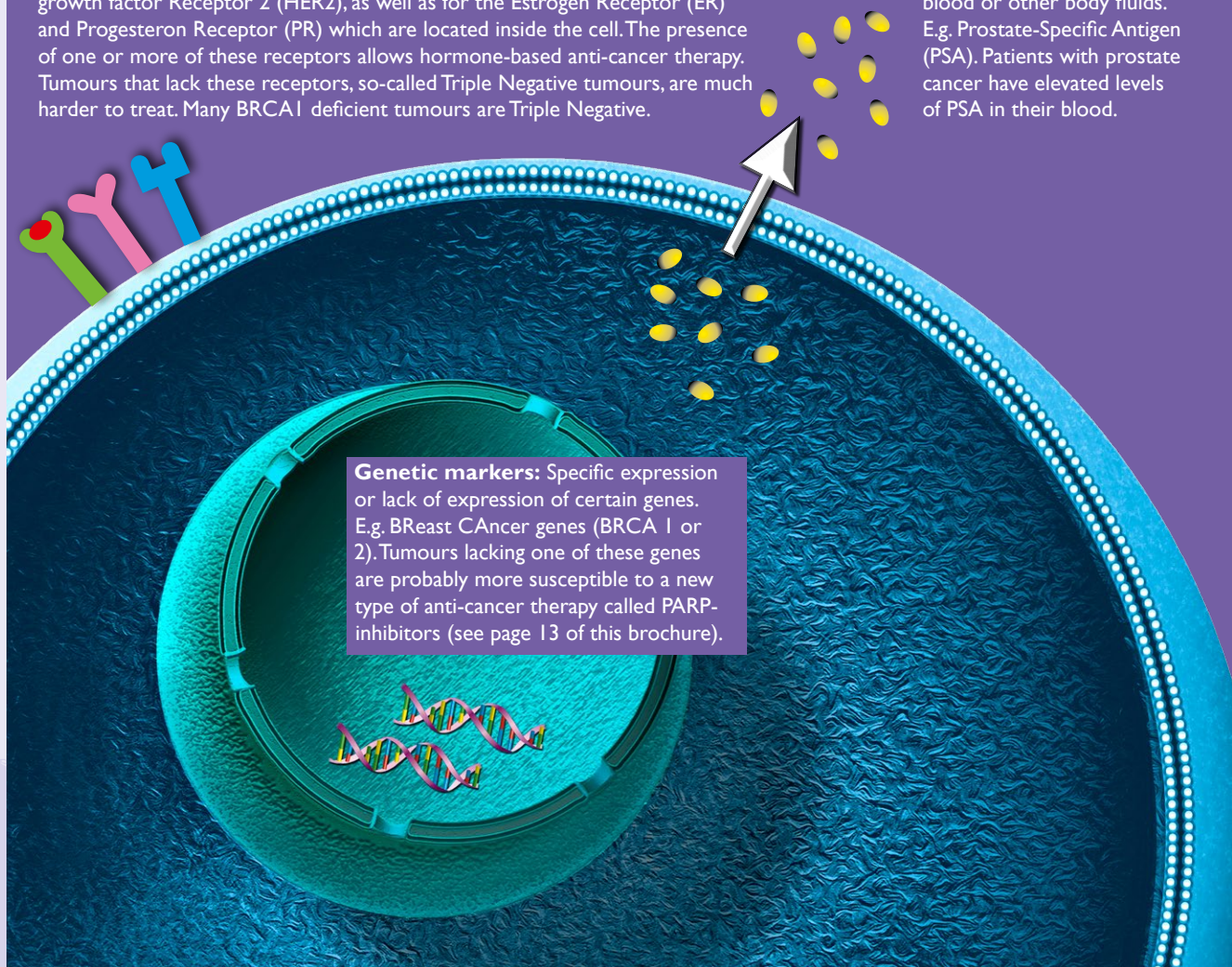
Biomarkers: A tumour's signboard

Even though tumours are better off unnoticed, most of them put out a sign in one way or the other. These signs are called biomarkers and they come in different forms.

Cell surface markers: Molecules specifically present on the surface of tumour cells. Breast tumours are routinely screened for the Human Epidermal growth factor Receptor 2 (HER2), as well as for the Estrogen Receptor (ER) and Progesteron Receptor (PR) which are located inside the cell. The presence of one or more of these receptors allows hormone-based anti-cancer therapy. Tumours that lack these receptors, so-called Triple Negative tumours, are much harder to treat. Many BRCA1 deficient tumours are Triple Negative.

Excreted markers: Biological molecules found in blood or other body fluids. E.g. Prostate-Specific Antigen (PSA). Patients with prostate cancer have elevated levels of PSA in their blood.

Genetic markers: Specific expression or lack of expression of certain genes. E.g. BRCA1 or BRCA2. Tumours lacking one of these genes are probably more susceptible to a new type of anti-cancer therapy called PARP-inhibitors (see page 13 of this brochure).



Chapter 2. If it runs in the family

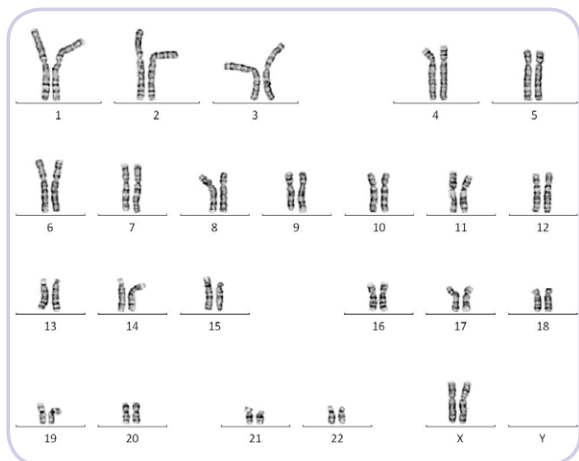
Your beautiful brown eyes. Your curly hair. The dimples in your cheeks. Your blood type. At birth you inherited a diverse set of visible and invisible traits from your parents. Some you might like a lot, some a little less. But what if you inherited a predisposition for breast cancer?



In Europe, the risk that a woman develops breast cancer in her lifetime is about ten percent. For some women, however, this risk is increased dramatically. Because of an inherited predisposition, they have a risk of developing breast cancer of sixty to eighty percent, often at a much younger age than average. What does that mean, an inherited predisposition to cancer?

Inevitable mistakes

A tumour consists of cells in which mistakes have accumulated in the DNA. Every single one of the billions of cells in our body contains about two metres of DNA. This DNA contains approximately 20,000 genes, regions in the DNA which influence a particular characteristic, e.g. eye colour or blood type. Each time a cell divides



the DNA is copied and distributed over the two new cells. Mistakes arise during the copying process, but also because of external factors such as exposure to UV light or certain chemicals. The vast majority of these mistakes are effectively repaired by the cell, but sometimes a mistake persists. Such a permanent change in the DNA is called a mutation. Mutations in specific genes are the cause of cancer.

A spare copy

Even though everybody acquires mutations in their DNA during their lifetime, the risk of developing cancer is relatively low, especially at a young age. That is because several different genes have to be mutated before cancer arises. Moreover, there are two copies of each gene in the cell. Only one of these copies is in use. If a mutation arises in one copy of a gene, the cell still has a spare gene to use so it can continue to function normally. Only if both copies of a gene are mutated, can cancer develop.

One point down

Some people, however, have a much higher risk of developing a certain type of cancer, as is the case for the women with an inherited predisposition for breast cancer. These women inherited a mutation from either their father or their mother in one of the Breast Cancer genes BRCA1 or BRCA2. All cells in their body therefore contain only a single intact copy of one of these genes. It is as if they are riding a bicycle with two brakes, one of which is already broken. Breast tumours will develop as soon as the second brake also fails, thus when the other copy of the BRCA-gene is also mutated.



Improving treatment

Treatment of hereditary breast cancer is no different from treating non-hereditary breast tumours. Scientific research, however, has shown that assessment of the genetic composition of tumours might be helpful in predicting individual responses to treatment and for counteracting side effects. Recent discoveries concerning the genes BRCA1 and BRCA2 indicate potential clues for the development of more tailor-made cancer therapies.

Chapter 3. Nature's handymen

"Whatever might be broken, we will fix it." That sounds like an advertisement from a handyman. But it could just as well be nature's slogan. For nature has provided our cells with clever mechanisms to monitor possible mistakes in our DNA and to cope with them.



Damage in our DNA can generally be repaired effectively. That is a good thing, since the DNA in our cells is damaged up to one million times a day, each day. Living would be utterly impossible if cells were not able to fix mistakes in their genetic material. That is why nature provided cells with effective repair troops.

Step-by-step

The DNA repair troops consist of multiple specialised proteins working together to repair the damage in a step-by-step fashion. Each protein specializes in a specific step. First, protein A recognises the damage. Then, several other proteins come to the spot to cut out the mistake. What remains is a gap in the DNA, which is filled by yet another set of proteins. Different repair troops cope with different kinds of damage, and together they can fix nearly everything.

Broken in two

But what does DNA damage repair have to do with breast cancer? We have to go back to the BRCA1 and BRCA2 genes to answer that question. As mentioned in the previous chapter, these genes are often mutated in familial breast cancer. To know what that means for the cells in the tumour, scientists determined the function of BRCA1 and BRCA2. They discovered that the genes encode proteins with an important role in repairing DNA damage. More specifically, these proteins are required for the repair of damage in which the long DNA molecule is broken in two, so called double strand breaks. These very hazardous breaks arise especially in cells that are duplicating their DNA in preparation for cell division. Although double strand breaks are very rare, repair of these DNA breaks is essential for cells to function properly.

Bad news and good news

In cells with a mutation in the BRCA1 or BRCA2 gene, repair of double strand DNA breaks is severely impaired. As a result, an accumulation of mistakes in the DNA will occur and these cells are therefore more likely to transform into a tumour cell. The lack of proper repair of double



strand breaks is bad news in terms of developing cancer. But it might potentially be good news in terms of cancer treatment, serving as a possible clue in the search for better and more specific anti-cancer treatments.

Repairing the damage: BRCA1 and BRCA2

Efficient repair of DNA damage is crucial for the survival of a cell. Cells have two ways of repairing the especially harmful double strand breaks: 'Quick and Dirty' or 'Neat and Clean'.

'Quick and Dirty': The fastest method to repair a double strand break is to simply 'glue' the two ends back together. The risk, however, is that small parts of the DNA break off and are lost. The repaired DNA will then contain a mistake.

'Neat and Clean': This method is more complicated and is therefore slower. It needs the aid of the second DNA copy in the cell. This copy is used as an undamaged template to fill the missing part that was lost during the double strand break.

Cells predominantly use the quick and dirty method. Under death threat, speed is obviously more important than accuracy. Only when the fast method is not possible, for instance when cells are copying their DNA for cell division, do they turn to neat and clean repair. The breast cancer genes **BRCA1** and **BRCA2** are both needed in the neat repair pathway. Cancer cells lacking one of these genes thus lack the possibility to repair double strand breaks during the preparation for cell division. Since cancer cells are actively dividing cells, this poses a serious threat to these cells.



Chapter 4. Finding the weak spot

Imagine you go skydiving without a reserve parachute. You will have a good chance of returning to the ground safely, since the risk of the main parachute failing is small. But what if it does fail?

If it does fail, you are in serious trouble. That also holds true for cells in a hereditary breast tumour. They lack an important DNA repair pathway which serves as the reserve parachute if another mechanism fails. Scientists think that this might be the weak spot to be targeted for developing a more specific therapy for this type of cancer. What do they have in mind?



Reserve parachute

DNA is a long molecule that looks like a twisted rope ladder. Damage can arise both in the steps of the ladder and in the ropes, called strands in the case of DNA. If a strand breaks, efficient DNA repair troops are usually on the spot to fix the damage instantly. If, however, the damaged strand is not repaired before the DNA is being copied, the end result is a DNA molecule with breaks in both strands. A severe situation, but nature would not be nature if it did not provide repair troops for that too, serving as the reserve parachute to save the cell.

Sabotage the main chute

In hereditary breast cancer patients who carry mutations in the genes BRCA1 or BRCA2, the repair of the harmful double strand breaks is lacking. The tumour cells will thus die when this type of DNA damage occurs. Double strand breaks, however, are very rare. Therefore cells

hardly notice the absence of the reserve parachute. So scientists are searching for a way to sabotage the main parachute, by inhibiting the repair of single strand breaks. If they succeed, the increased number of double strand breaks will be lethal to the tumour cells. Healthy cells do have the reserve parachute, so they will not suffer from the treatment.

More patients

For hereditary breast cancer, the search for an effective saboteur of the main parachute looks promising. This is good news for patients, even though it will still take quite a while before they will benefit (see Chapter 5). However, the group of women suffering from familial breast cancer is small compared to the total number of breast cancer patients. The next challenge is obviously to increase the group of cancer patients benefiting from these findings. Scientists are therefore searching for other combinations of cellular processes that act as each other's safety parachutes - or for other mutations in tumour cells that indicate they might be sensitive to the same drug as BRCA1/BRCA2 deficient tumour cells.

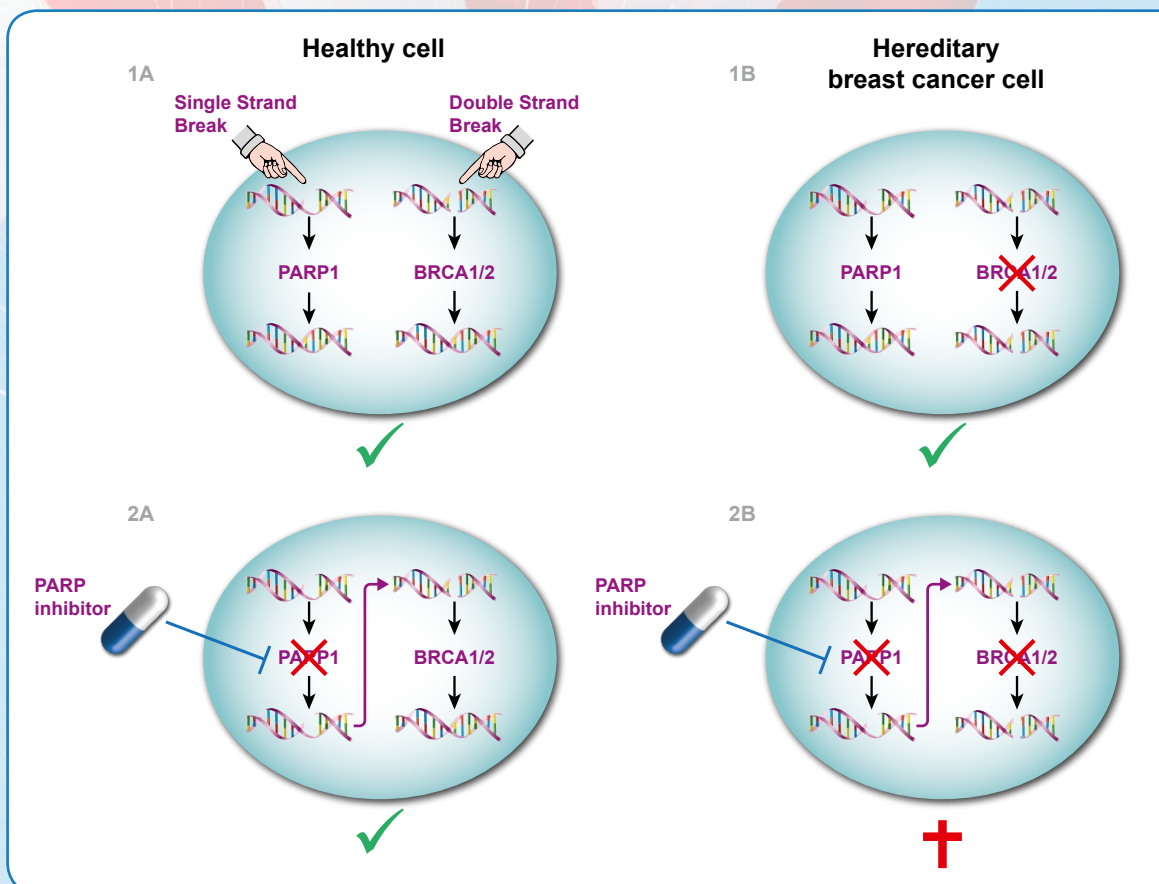


PARP inhibitors: aiming for the cancer cells

Many types of chemotherapy kill cancer cells by causing DNA damage. Unfortunately, they also harm healthy cells, causing detrimental side effects. A new drug, called PARP inhibitor, circumvents this problem by aiming specifically for the weak spot in hereditary breast cancer.

Healthy cells possess different mechanisms to repair the various types of DNA damage. For instance they repair double strand breaks using **BRCA1** and **BRCA2** (Figure 1A), while they repair single strand breaks using **PARP1** (Figure 1B). Breast cancer cells with a mutation in **BRCA1** or **2** cannot repair double strand breaks, but they are still able to repair the more common single strand breaks.

A **PARP inhibitor** prevents the repair of single strand breaks in both healthy cells and cancer cells. Unrepaired single strand breaks are prone to change into the more hazardous double strand breaks when cells duplicate their DNA in preparation for cell division. No problem for healthy cells, because they can still repair these breaks using **BRCA1** and **BRCA2** (Figure 2A). But **BRCA1** or **2** deficient cancer cells cannot repair the increased number of double strand breaks, resulting in cell death (Figure 2B).



Chapter 5. Potential patient benefits

In the quest for new or improved cancer therapies, one must be prepared for a long haul. The sole identification of a target is not enough for a new drug to be developed and registered. What are the odds for patients suffering from (hereditary) breast cancer or related cancer types?

One might think that with the discovery of a potential new target for treatment, that the end is in sight. Patients will soon benefit from such a discovery. Unfortunately, this is not always the case. The target has to be checked and double checked in numerous experiments and multiple phases of clinical trials have to be successful. Only if the new treatment really adds to the existing treatments, will it be added to the palette of anti-cancer therapies. In the case of familial breast cancer, a number of essential questions still have to be answered.



Do more patients survive because of the new treatment?

Most current therapies for breast cancer are not adjusted to the genetic characteristics of the tumour. Nonetheless, as a result of these treatments a vast number of patients can be cured. But unfortunately not all. The chance of surviving breast cancer is highly dependent on when the patient is diagnosed. Late discoveries increase the risk of metastases and especially metastasised breast cancer currently has a bad prognosis. New treatments are therefore desperately needed.

The new target for treatment, aiming specifically for the reserve parachute of the tumour cells, is promising. It has been tested in animal models and in cells taken from patients. The effects were very clear. Several clinical trials have also been executed, in which patients were included who had already been treated with traditional anti-cancer therapies. The overall results of these trials indicate that some, but not all, patients

benefitted significantly from the new treatment. Unfortunately, the group of patients in the trial is too small to draw real conclusions. The results need to be confirmed in larger groups of patients, and the optimal treatment still needs to be determined. It is therefore too early to tell whether the new treatment is an actual improvement over the existing anti-cancer treatments.

Does the new approach significantly decrease the negative side effects of treatment?

One of the difficulties with traditional anti-cancer therapy is the vast number of negative side effects. This is predominantly caused by the fact that healthy cells also suffer from the treatment. In the clinical trials applying the new treatment, relatively mild side effects are being reported compared to the often detrimental side effects of traditional chemotherapy or radiation therapy. This suggests a reasonable improvement in the quality of life, both during and after treatment.



Taken together, the laboratory results and the results of the clinical trials sound promising. Based on the results so far, it is unfortunately too early to predict when the new treatment will be made available. The current challenge is to optimise the treatment further and to improve the possibilities to select patients that will benefit from the treatment. Scientific researchers in academia and pharmaceutical companies join forces to face this challenge and to find the best combination of the new treatment with existing chemotherapeutic agents.

Drug development: from laboratory to patient

Developing a new drug and bringing it to the market is a lengthy process which may take several years or even decades. It can be divided into pre-clinical and clinical phases.

Pre-clinical phase:

The pre-clinical phase starts with the discovery of a chemical substance with promising activity against a particular biological target thought (or known) to be important in disease. A wide range of laboratory experiments follows to:

- Determine the safety and toxicity.
- Further investigate the way the substance works. What exactly does it do inside cells? How fast do cells break it down? Et cetera.
- Make a recommendation of the dose and administration scheme for the first clinical trial.
- Determine the chemical composition, stability and solubility.
- Optimise the manufacturing process to allow scaling of the production from milligrams in the laboratory to tons in the pharmaceutical factory.
- Examining whether the substance is suitable for producing in capsules, tablets or injectable formulations.

Clinical phase:

The information from all pre-clinical tests is submitted to regulatory authorities and only upon approval, drug development moves into the clinical phase. In that case a series of clinical trials is performed to determine the effectiveness and safety of the new drug in humans (see 'Clinical Trials' below).

Clinical trials: Check and double-check

Before a new drug is brought to the market it has to pass a series of clinical trials. These are tests to determine whether the drug has the expected health effect and if the drug is safe to use. Clinical trials are classified into five phases. Drug development can be aborted at any point during these phases, if the drug is not as safe or effective as expected.

Phase 0: Biological effect

These are the first trials in humans. A small number of healthy volunteers (10-15) are given small doses of an experimental drug. Researchers monitor the effect of the drug in the body of the volunteer (pharmacodynamics) and how the body handles the drug (pharmacokinetics).

Phase 1: Safety

A slightly larger group of healthy volunteers (20-80) test the experimental drug or treatment. During this phase the safety is evaluated, a safe dose range is determined and side effects are identified.

Phase 2: Treatment protocol

The experimental drug or treatment is given to patients with a specific disease or medical condition rather than healthy volunteers, to determine its effectiveness and evaluate its safety further.

Phase 3: Final testing

By giving the drug to a larger group of selected patients, researchers aim to confirm the effectiveness and to compare it to commonly used treatments. They will also monitor side effects and other aspects important for safe use of the drug.

Phase 4: Post-approval studies

These studies might yield valuable refined information on the drug's benefits, side effects and optimal use.

Some Phase 2 and most Phase 3 trials are designed as randomised, double-blind and placebo-controlled:

Randomised: It is randomly assigned whether a participant receives the experimental drug or a placebo.

Double-blind: To exclude any possible bias in the results, both participant and clinician do not know whether the treatment which has been given is the experimental drug or the placebo. Another option is a 'double-dummy' test, in which all participants receive both placebo and the drug to be tested in alternating periods of time.

Placebo-controlled: A placebo is a fake treatment that is used to distinguish the effect of the drug from any effect of the treatment itself.

A drug that successfully passes phases 0, 1, 2 and 3 will usually be approved for use by the national regulatory authority.



Colofon

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