7

Clinical Development Paradigms for Cancer Vaccines: The Case of CIMAvax EGF®

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1. Introduction

Scientific progress is inhabited by paradigm shifts. In 1962, Tomas Kuhn popularized the concept of ¨paradigm shift¨ arguing that scientific advancement is not evolutionary, but rather is a "series of peaceful interludes punctuated by intellectually violent revolutions", and in those revolutions "one conceptual world view is replaced by another" (Kuhn, 1962).
Again according to Kuhn, ¨paradigm shifts occur when anomalies in the old paradigm accumulate and cannot be overlooked anymore¨. This is probably the situation today in the treatment of advanced cancer.
However, changes are difficult. Human beings resist changes.
For many years, chemotherapy has been the gold standard of cancer therapy. The era of cancer chemotherapy began in the 1940s with the first use of nitrogen mustards and folic acid antagonist drugs (De Vita et al, 2005) and a major break-through in 1965, when James Holland, Emil Freireich, and Emil Frei hypothesized that cancer chemotherapy should follow the strategy of antibiotic therapy for tuberculosis with combinations of drugs, each with different mechanisms of action (Frei et al, 1965). Cytotoxic chemotherapy in fact succeeded in producing major therapeutic effects, including cures, in hematological malignancies and some solid tumors such as testicular and ovarian cancers. However its contribution to the treatment of most solid tumors has been much less. The success history of chemotherapy in leukemia and lymphoma simply did not repeat in most solid tumors.
Chemotherapy has the disadvantage of its high toxicity, because is an unspecific treatment which effect does not distinguish between normal and tumor cells.
The paradigm of selective killing of cancer cells in a way alike to what antibiotics do for infections, created in turn a standardized procedure for stepwise drug development through conventional Phase I, II and III trials, which was soon adopted and translated into regulations by many drug regulatory authorities. The designs of these clinical trials respond to the need of demonstrating the drug efficacy at its maximal tolerable dose (MTD).
However, although retaining the main concept and adapting to the old paradigm malfunctioning, variants have been introduced for cancer drugs approval: i.e. approvals without randomized trials and approvals based in accelerated approval regulations.
From January 1973 through December 2006, 68 new drugs were approved for cancer therapy from which 31 were approved without 2 arms randomized clinical trials including a control arm with different therapy, supportive care or placebo (Tsimberidou, 2009).

Accelerated approval (AA) regulations were established by the US Food and Drug Administration (FDA) designed to shorten development times of drugs for serious medical diseases, i.e. cancer (Dagher et al, 2004; Richey et al, 2009). According these, drugs received AA based in Phase II trials and sponsors must confirm efficacy in post-approval trials. Since the first AA for an oncology indication was granted between 1995 and 2008, 51 new molecular entities have received FDA approval for cancer therapeutic indications: 32 with regular approval and 19 with AA (Richey et al, 2009).

In some way, regulations have moved towards faster access to patients of even the very toxic chemotherapies.

Biotechnology development has provided new therapeutic weapons for cancer therapy. According Pharma 2009 report, there are currently 633 biotechnology medicines under development, from which 254 are for cancer therapy (109 monoclonal antibodies and 63 cancer vaccines). That means, 40% of worldwide biotechnology is cancer therapy.

These Biotechnological products have the characteristics of being highly specific which in turn causes a low toxicity, long-term usability and usability in combinations.

Biotechnology anticancer drugs are not just more drugs, they are different drugs; and their entrance into cancer therapy high lightened the limitations of the prevalent paradigm for drug development. The enormous differences between the new biotechnological products and chemotherapeutic agents, makes necessary changes in established clinical development paradigms. Specifically, for cancer vaccines, more flexible and focused developmental guidelines are needed to address their unique characteristics (Hoos et al, 2007).

In this report we use the case of CIMAvax-EGF® to illustrate the operation of the emerging paradigms.

2. Conventional clinical development paradigm for anti-cancer chemotherapeutics

Cancer drugs development paradigms have been based on criteria adjusted to cytotoxic agents. These criteria were not always transparent in the literature, but they basically are the following:

- Maximizing dose should maximize efficacy.
- Pharmacokinetics is relevant to dose finding.
- Objective response predicts survival (SV) and clinical benefit.
- Tumor shrinkage is expected to occur fast.
- Objective progression indicates treatment failure (drugs are not active if the tumor is growing).
- Drugs to be tested in combination must be active as single agents.
- Patient population for clinical trials must be as homogeneous as possible.
- Drugs must be tested first in advanced disease and moved to ¨adjuvant setting¨ (seeking cures).

According these criteria, clinical trials have been designed and classified into different phases, covering the different questions to be answered about drugs under development.

Considering the high toxicity of cytotoxic agents, and considering the concept that maximizing doses should maximize efficacy, Phase I are dose escalation trials, designed for testing pharmacokinetics and MTD. Dose escalation in Phase I trials gives data about the maximal dose which could exert a therapeutic effect without severe damage due to

excessive toxicity. The effective time of the drug in circulation has to be studied in pharmacokinetics studies, and this has been an additional goal of Phase I clinical trials.
Once defined the drug dose, a proof of clinical benefit is the next step. Currently, this is measured as objective response (assessing tumor shrinkage), because cytotoxic drugs are expected to decrease the tumor mass. Phase II trials are designed and conducted to find this kind of anti-tumor activity in some specific patient population. These trials are usually not randomized and evaluate the tumor response according to RECIST criteria (Response Evaluation Criteria in Solid Tumors). They include the minimal patient population required to show statistical significance of a given percentage of tumor response which is different from zero.
When the product under study demonstrates to have anti-tumor activity, randomized Phase III trials are then designed to compare the new drug with the currently accepted standard therapy.
If a novel chemotherapeutic agent is more efficient and/or has better safety profile than a previous one, it is considered to substitute the previous therapy or to add on it. Usually, a large number of patients are required to achieve statistical power to detect small differences between randomized groups.
It is this statistical significance of therapeutic effect in Phase III clinical trials which guarantee the Regulatory Approval. Nevertheless, the limitations of this stepwise process have driven regulatory adaptations such as the concept of AA after an obviously successful Phase II Trial. This concept has had diverse expressions and nuances in different regulatory authorities.

3. A clinical development paradigm shift is needed for cancer vaccines: Why?

Therapeutic cancer vaccines are active immunotherapy approaches that provoke an immune response against antigens relevant for tumor cell survival or growth (Talucka, 2011). As their action is very specific towards the cancer associated antigen, cancer vaccines has very low toxicity profiles. That makes possible long lasting use as well as combination with other drugs. In general, not tumor shrinkage is expected, but a prolonged patient´s survival as a consequence of disease control with chronic vaccinations compatible with good quality of life (Lage & Crombet, 2010).
In this very different scenario, the development paradigm used for chemotherapeutics is not working well (Table 1):

- In cancer vaccines the MTD is not always the optimal dose.
- Objective response according to RECIST is not always a good predictor of **SV**.
- Therapeutic benefit could be delayed on time.
- Cancer vaccines could be active even beyond progression.
- Combinations can be effective using drugs that are not active as single agents.

The first trials with cancer vaccines are mainly devoted to demonstrate the proof of the therapeutic principle, i.e. immunogenicity of the vaccine preparation, eliciting an immune response to the antigen they are intended to target; and they are also used for testing different formulations, doses, schemes and, by sure, safety. The novel paradigm of clinical development of cancer vaccines makes then Phase I trials better defined as Proof of Principle trials (PPT).

For cytotoxic drugs, tumor reductions are expected and objective responses predict clinical benefit. In cancer vaccines it has been demonstrated that objective response is not always a good SV predictor; and therefore SV remains the appropriate end point. For SV analysis, comparison between randomized vaccine and control groups is required. Then after PPT, cancer vaccines moves directly towards randomized trials to test the efficacy of the product.

General principles that have ruled oncology drug development.	Why these principles are not well adapted to cancer vaccines
The increase in dose should increase efficacy.	Maximal tolerated doses are not optimal doses. Due the low toxicity of cancer vaccines, it is not evident that a maximal tolerable dose will be coincident with the optimal dose to reach the vaccine effect, which could be much lower.
Pharmacokinetics is relevant for finding optimal dose.	
Objective responses predict clinical benefit.	Objective response is not a good SV predictor. Not necessarily, a patient with objective response has increase SV, which is the most important factor for the cancer patient.
A fast tumor reduction is expected.	Therapeutic benefit could be delayed on time. Cancer vaccines require some time to exert their effect, unlike cytotoxic drugs that provokes an immediate cell destruction effect.
An objective progression is considered a treatment failure. Drugs are NOT active if the tumor is growing.	Cancer vaccines could be actives even beyond disease progression. Progression doesn´t means less effectiveness of the vaccine, measured by increase in SV, which could be reached by slower progression related with a good quality of life.
Drugs assayed in combination must be individually actives.	Therapeutic vaccines can be effectives in combinations with other onco-specific drugs, even when not individually active. They can be used additionally and not instead of other therapies.

Table 1. Why general principles that direct oncologic drugs development does not apply to cancer vaccines?

As can be realized, these trials do not fulfill the characteristics of classic Phase II trials defined for cytotoxic drugs, firstly because the end point is different, and secondly because are already randomized trials.

In the novel paradigm for cancer vaccines, these trials are called ¨Efficacy trials¨ (ET).

The number of patients in these trials is adjusted to show statistical significance of a therapeutic advantage which is considered medically meaningful. With a wise medical judgment of what is medically relevant these ET could be often smaller to the current Phase III trials of the classic paradigm.

Such an emerging paradigm for the development of cancer vaccines should also translate into the attitude of Regulatory Authorities for granting Registration.

4. CIMAvax EGF®: Immune response translates into clinical impact

The need of a new paradigm for cancer vaccine development can be illustrated by the story of CIMAvax EGF®, a therapeutic vaccine recently registered in Cuba for advanced lung cancer (Gonzalez et al, 1998, 2003, 2007, 2011; Lage et al, 2003; Crombet et al, 2006; Gonzalez & Lage, 2007; García et al, 2008; Neninger et al, 2008a, 2008b; Rodriguez et al, 2010).

Endocrine therapy is an old and well validated approach for cancer treatment. Some tumors are considered as hormone-dependent because they require hormone stimulation for the continued growth of the tumor cells. In such cases, cancer bearing patients may benefit from hormone therapy, mainly based in deprivation of hormonal stimulus by different procedures.

But in addition to sex steroid hormones, tumor can be regulated by growth factors, such as EGF, through the binding to their receptors and activation of phosphorilation cascades leading to tumor cell proliferation. Currently, research in new anticancer drugs is increasingly focused in growth factors, their receptors and signal transduction mechanisms. Active and passive immunotherapies can be instrumental in the aim of interfering growth-factor stimulation of cancer cell proliferation. (Gonzalez & Lage, 2007).

The Epidermal Growth Factor(EGF) based cancer vaccine (CIMAvax EGF®) is a conjugate of human recombinant EGF with the P64K protein of *Neisseria meningitides* (acting as a carrier protein) (Rodríguez et al, 2008). It was designed to induce specific anti-EGF antibodies (Abs) which, in turn, recognize and bind circulating EGF, avoiding further binding to the cell membrane receptor (EGF R).

These ligand /Ab unions, forms immune-complexes that are eliminated from the circulation through the liver, as other immune-complexes do (González et al, 1996). As can be realized, it is like an immune-castration effect, more similar to some hormone-therapies approaches aiming to deprive the cells of the hormone, but with the difference that it is the self immune system which deprives the growth factor (EGF).

This vaccine is not meant to destroy the tumor by inducing immune effectors mechanisms, but to inhibit further tumor cell growth. This completely different mechanism of action could not only stop tumor growth, but could shift the balance between uncontrolled proliferation and cell death.

Anti-EGF Abs are then a main marker of response to vaccination. This has been verified in the clinical setting by the observation that patients with higher anti-EGF Ab titers survived significantly more than patients with low anti-EGF Ab titers.

5. How CIMAvax EGF® moved through clinical development: Applying the paradigm shift

The clinical development of CIMAvax EGF began in 1995. From then up to date, more than 1000 advanced cancer patients have received this vaccine.

Our very first objective was to demonstrate that the vaccine elicited anti-EGF Abs as it was designed to do. Clinical trials (Table 2) where then designed to demonstrate that the vaccine was immunogenic and provoked a depletion of circulating EGF. All trials have also safety as primary objective.

Different formulations, schemes and doses of the vaccine were tested and related with immunogenicity and safety.
As can be realized, these trials were not designed with the main goals of Phase I trials defined for cytotoxic drugs (pharmacokinetics and definition of maximal tolerable dose). Trials designed for this vaccine can be better called PPT.
Five PPT were performed allowing the selection of the optimal formulation, scheme and doses for moving forward to the ET.
In the first clinical trial, 10 patients with epithelial tumors were enrolled. Patients received two single doses of the vaccine composed by human recombinant EGF coupled to either Tetanus Toxoid (hu-r-EGF-TT) (5 patients) or the recombinant P64K protein from *Neisseria meningitidis* (hu-r-EGF-P6K) (5 patients), both groups used aluminum hydroxide (alum) as adjuvant. Each single dose of the vaccine was given on days 0 and 14.

Clinical trial	Target population	End point	Reference
PPT Exploratory trial (1)	Solid tumor patients (n=10)	Carrier selection (TT vs. P64)	Ann Oncol 1998;9(4):431
PPT Exploratory trial (2)	NSCLC patients (n=20)	Adjuvant selection (Alum vs. Montanide)	Ann Oncol 2003; 4(3):461
PPT Exploratory trial (3)	NSCLC patients (n=20)	Cyclphosphamide (CPM) pre-treatment (CPM or not)	Ann Oncol 2003; 4(3):461
PPT Exploratory trial (4)	NSCLC patients (n=20)	Dose escalation (2 doses)	Cancer Biol Ther. 2006; 5, 15.
PPT Exploratory trial (5)	NSCLC patients (n=20)	Schedule evaluation Vaccine-Chemotherapy-Vaccine	J Immunother 2009;32:92–99
ET (6)	NSCLC patients (n=80 s)	SV benefit Vaccine vs. BSC (2nd line therapy)	J Clin Oncol. 2008 6(9):1452.
ET (7)	NSCLC patients (n=579)	SV benefit Vaccine vs. BSC (2nd line therapy)	Ongoing, not published.

Table 2. Clinical trials of CIMAvax EGF

The main objectives of the trial were to look at safety and immunogenicity of vaccination with self EGF in humans as well as to compare between the 2 carrier proteins: TT and P64K. Following vaccination there were no significant adverse events. Seroconversion (defined in this study as a doubling of Ab titer above baseline) was reported in 6 of the 10 patients included in the trial.

Both Tetanus Toxoid and P64K protein from *Neisseria meningitides* showed carrier effect. In each of both treatment groups 60% of patients developed anti-EGF Ab responses after immunization. However, the Ab response against the TT in the group of patients vaccinated with hu-r-EGF-TT was very high, but not the Ab response against P64K in the group of patients vaccinated with hu-r-EGF-P64K. Trying to avoid any phenomenon related with epitopic suppression, P64K was selected as carrier protein for further trials (Gonzalez et al, 1998).

The second clinical trial was designed to demonstrate the safety and immunogenicity of the EGF based cancer vaccine using two different adjuvants: aluminum hydroxide (alum) or Montanide ISA 51 (Seppic, France). In this case, 20 stages IIIb-IV NSCLC patients were enrolled in the trial one month after concluding their first line chemotherapy, and then randomized for the adjuvant to be used. Ten patients received the conjugated vaccine in alum and 10 patients in Montanide ISA 51 as adjuvant.

A secondary aim of this study was to evaluate the effect of 5 single doses of the vaccine in the induction period (days 0, 7, 14, 21 and 51) so as of re-immunization when antibody titers decreased to, at least, 50% of their peak titer reached at the induction phase. Also the relation between anti-EGF antibody titers and patient's SV was evaluated (Gonzalez et al, 2003).

The third clinical trial had the very same design that the second one, but all patients in both treatment groups, received a low dose CPM as an immune-enhancer, 100 mg/m^2 body surface area 3 days before starting vaccination schedule. (Gonzalez et al, 2003).

In both, second and third trials, sera were collected on days 0, 14, 28, 60 and then monthly for anti-EGF Ab titers determination. Tumor response was evaluated on the first month after inclusion and then, every 3 months, by chest X-ray, abdominal ultrasound, and thoracic and abdominal computerized tomography (CT) scan. Objective responses were classified according to the WHO criteria.

Pooled results from both trials were analyzed looking for immunogenicity, safety and effect of EGF vaccination on SV in the different treatment groups. (Gonzalez et al, 2007).

For immunogenicity analysis, two variables were analyzed: % of patients able to develop an Ab response as well as Ab titer levels.

Patients able to develop an Ab response after vaccination were grouped as:

1. Patient that seroconverts.
2. Good Antibody Responders (GAR).
3. Poor Antibody Responders (PAR).

According to this classification, the higher % of either, seroconversion and GAR, were obtained in the groups of patients using Montanide ISA 51 as adjuvant. Cyclophosphamide pre-treatment did not show any improvement regarding % of seroconversion neither % GAR. It was concluded that the use of Montanide ISA 51 as adjuvant with the EGF vaccine improves % of anti-EGF Ab responder's patients.

When analyzing Ab titer levels in responder patients, measured as geometric means of sera dilutions, an improvement was observed when Montanide ISA 51 was used as adjuvant. Pre-treatment with cyclophosphamide also improved the Ab titer levels.

Taken together, the data from both trials indicates that, regarding immunogenicity (% of responders and Ab titer levels), the best results were obtained when using Montanide ISA51 as adjuvant and cyclophosphamide pre-treatment.

The kinetics of anti-EGF Ab response was also studied. Re-immunizations when Ab titers decreased did not provoked a characteristic booster effect (stronger and maintained Ab responses). Ab titers increased after re-immunization but only to the same levels reached as previous maximal values and decreased again in a short period of time. It is likely to confirm that continuous re-immunizations were needed to maintain anti-EGF Ab titer levels.

Results showed a significant increase in SV for GAR as compared with PAR and with an historical control group (Table 3). In pre-clinical studies, we demonstrated a direct relation between anti-EGF Ab titers and SV in tumor challenged mice (González et al, 1996). The results obtained from clinical trials indicate that a similar association occurs in vaccinated cancer patients.

SV	Mean (months)	Median (months)	p (log rank test)
GAR	12,41	9,41	P<0,05
PAR	5,47	4,5	
Historical control group	7,41	5,67	

Table 3. Relation between Ab titers provoked by vaccination and patient´s survival in 2nd and 3rd clinical trials with the EGF based vaccine.

One of the patients that reached a maintained high anti-EGF Ab response showed a tumor regression on month 12 after receiving the first vaccination. This is a single case and should be looked carefully, but it should be noted that this was one of the patients that developed higher and maintained anti-EGF Ab titers after vaccination.

No evidence of severe clinical toxicity was observed. Secondary reactions were mild or moderated, limited to 14 of 40 patients. Main reactions consisted on chills, fever, vomits, nausea, hypertension, headache, dizziness, flushing, and pain at the site of injection, bone pain, mouth dryness or hot flashes that, in all cases, disappeared after medication. Hematological data and blood chemistry remained within normal ranges during the immunization and follow-up period.

A fourth trial was then designed, in this case an scale up dose Phase I trial, in which patients were randomized to receive a single dose of the conjugate vaccine hu-r-EGF-P64K in alum as adjuvant (10 patients) or a double dose of the same vaccine (in alum also) in 2 injection sites (10 patients). The immunization schedule consisted in 5 immunizations with the vaccine (single or double doses), on days 0, 7, 14, 21 and 28, and then monthly re-immunizations. This trial was further extended to include 0 more patients (10 in each group) (Crombet et al, 2006).

Regarding immunogenicity, improved results were obtained in patients receiving double doses of the vaccine, considering Ab titer levels (sera dilution geometric means).

In this trial, EGF levels in sera were also tested. An inverse correlation was observed between EGF levels in patient sera and anti-EGF Ab titers. This result agrees with the vaccine working hypothesis. Anti-EGF Ab should bind to circulating EGF provoking a decrease in the EGF concentration. Less (or none) EGF is available to bind the EGF receptor, avoiding then the proliferation mechanisms derived from such binding.

Patients in the double dose group reduced more their EGF sera concentration that patients in the single dose group.

Again a significant increase in SV was observed for GAR as compared with PAR (Table 4).

Additionally, in these trials EGF sera levels were measured. A significant increase in SV was directly correlated with decreased EGF blood levels. Vaccinated patients with an EGF sera concentration after vaccination ≤168 pg/mL showed a significant increase in SV as compared with patients with levels >168 pg/mL ((Table 4). This is also an important result, and could means that EGF levels can be considered as an adequate surrogated marker of anti-tumor response.

There was a trend to increased SV in patients in the double dose group as compared with patients in the single dose group.

According to the results obtained from the previous trials, it was decided to move forward with the vaccine formulation composed by EGF-P64k in Montanide ISA 51 as adjuvant (CIMAVAX EGF) in a scheme including pre-treatment with low dose of cyclophosphamide.

A trial was designed where 80 patients, 1 month after concluding their 1rst line chemotherapy, were randomized in 2 groups, one receiving the vaccine CIMAvax EGF and the other only Best Supportive Care. According to the statistical design, with this small size randomized trial we expected to find a statistical improve in survival of 4 month for vaccinated patients as compared with the non vaccinated controls. An induction step of five single doses were given on days 0, 7, 14, 21 and 51, followed by monthly re-immunizations (Neninger et al, 2008a)

SV	Mean (months)	Median (months)	p (log rank test)
GAR	17,1	11,87	<0,05
PAR	7,84	7,07	
EGF sera concentration ≤168 pcg/ml	15,28	11,3	<0,05
EGF sera concentration >168 pcg/ml	5,79	5	

Table 4. Relation between Ab titers, sera EGF concentration and SV in the 4th clinical trial with the EGF based vaccine.

It is evident that this trial design does not correspond with the Phase II trials currently used for testing chemotherapeutics. It was called our first ET.

Results from this trial showed that, the% of patients that seroconverted (2X original anti-EGF antibody levels) or GAR, was significantly greater in vaccinated patients than in controls. The 50% of vaccinated patients were GAR. Serum EGF concentration was significantly lower in vaccinated patients than those in controls. That means, the vaccination generates anti-EGF antibody titers and decreases the EGF sera concentration.

It was also demonstrated that anti-EGF Ab titers correlates with decreasing EGF serum concentration in the vaccine group, but not in the control group.

Again it was corroborated that SV in GAR patients was significantly longer than in PAR patients. Additionally, there was a statistical difference in SV between vaccinated and control patients inside the GAR group but not inside the PAR group

Survival in patients with lower EGF sera concentration was longer than in patients with higher sera EGF concentration. There was a significant increase in SV between patients that

reached EGF sera concentration levels below168 pcg/ml as compared with patients didn´t reached these levels.

There was a trend toward better SV in vaccinated patients as compared with controls, which becomes significant when considered only those patients younger or equal 60 years old. Vaccination efficacy was well demonstrated in this patient cohort.

Differences in SV were much more advantageous for vaccinated patients when considered, for both vaccinated and controls, only those patients' responders to the first line of chemotherapy, but the trial has not a design strong enough to make the difference significant. Also in those patients with performance status (PS) 0 or 1 the effect of vaccination in SV was stronger. Again, the small sample number didn´t allow finding a statistical significance.

Summarizing we were looking an advantage in SV for vaccinated patients over non vaccinated controls that become increased in some patient niches, such as age under 60 years old, response to chemotherapy and PS.

At our experience, once safety of the vaccine is established, PPT needs not to be consecutive.

After concluding the patient recruitment in our first ET, we decided to design and perform a new PPT to test the optimal conditions that, up to this date, given the best results regarding immunogenicity (Neninger et al, 2008).

This trial design included:

1. Use of Montanide ISA51 as adjuvant and cyclophosphamide pre-treatment.
2. Four single doses of the vaccine given in 4 different anatomical sites.
3. Time intervals between vaccinations of 14 days.
4. Vaccine-Chemotherapy-Vaccine (V-Ch-V) approach: That means, a previous vaccination induction step on days 0 and 14 (4 single doses in 4 injection sites) is given before the first line of chemotherapy, then, after chemotherapy, vaccinations continue, 4 single doses (in 4 injection sites) each 14 days and then monthly.

With this immunization schedule, a huge improvement in immunogenicity was observed with 95 % of patients reaching the GAR condition and up to 20 fold increase in anti-EGF titers as compared with the levels previously obtained.

Because of the high anti-EGF antibody levels, an additional classification of immune response was considered. Patients were considered super Gar (sGAR) when reached anti-EGF Ab titers of 1:64,000 or more. The 55% of patients in the trial reached this condition while only 2,8% did in the previous Efficacy trial..

The association between Ab response and survival was corroborated in this series, where sGAR patients survived significantly more than GAR patients.

In all patients vaccinated under this V-Ch-V scheme, the EGF sera concentration decreased to 78 pcg/mL (baseline of the detection kit).

All vaccinated patients survived significantly more than the control group of the phase II trial.

From this trial, it was demonstrated the possibility of given 4X the vaccine dose used in the first efficacy trial, and the significant improvement in immunogenicity and EGF depletion that such scheme produced.

It was then designed a new trial, where, taking into account the results from both, the first ET and the fifth PPT, Five hundred and seventy nine patients were selected after being responsive to the first line of chemotherapy and subsequently stratified per age. One hundred ninety eight patients were included in the group of age equal or minor to 60 years old (strata 1) and 381 patients in the group of ages older than 60 years old (strata 2). After

stratification, patients were randomized for receiving vaccination or only Best Supportive Care. All patients received a 4X vaccine dose administered in 4 injection sites.
The sample size was calculated taking into consideration previous results and considering a 3 month of increase in SV for vaccinated patients in the strata 1 and 2 months of increase in survival for vaccinated patients in the strata 2.
As may be noticed, this trial design corresponds to a second ET that aimed to corroborate the results of our first ET results optimized conditions.
This trial is currently ongoing and a partial cut on the results according to the statistical design is very encouraging.
As well as the classical Phase I-II-III paradigm, the new sequence of cancer vaccine clinical trials also approaches the goals of understanding safety and efficacy. In such a way, the commonly called Phase I and Phase II clinical trials matches with PPT, while Phase III trials matches with ET.

6. The relationship between clinical trials and "levels of Evidence" CIMAvax EGF® example

In the last decades, as the emergence of new medical technology accelerates, there has been a growing claim to assess and to classify emerging knowledge according to the strengths of the evidence (Elstein, 2004)
A "Level of Evidence" ladder has emerged as follows:
Evidence level Ia: The evidence comes from a meta-analysis of randomized, controlled, well designed trials.
Evidence Level Ib: The evidence comes from, at least, one randomized, controlled trial.
Evidence level IIa: The evidence comes from, at least, one controlled, well designed, not randomized trial.
Evidence Level IIb: The evidence comes from, at least, one study not completely experimental, well designed, as cohort studies. Is referred to the situation when the application of an intervention is out of the investigators control, but whose effect can be assessed.
Evidence Level III: The evidence comes from studies of well-designed non-experimental descriptive, such as comparative studies, correlation studies or case-control studies .
Evidence level IV: The evidence comes from documents or opinions of expert committees or clinical experience of prestigious authorities or series of cases.
Levels of evidence then translate into the strength of recommendation that can be assigned to a given new technology.
A: Evidence level I: Highly recommended
B: Evidence level II: Favorable recommendation
C: Evidence level III : Recommendation favorable but not conclusive
D: Evidence level IV: Expert consensus without adequate research evidence.
During the clinical development of CIMAvax EGF®, the vaccine has transited through different stages of clinical trials and through different Evidence levels (Table 5).
We can conclude that CIMAvax EGF has 5 PPT, 2 ET (one ongoing) and has reached a level of evidence Ib that makes it highly recommended for its use in patients.
In summary, the historical development of CIMAvax EGF, illustrates the new development paradigm for cancer vaccines.
Firstly, the vaccine dose and schedule was selected across 5 different PPT, considering the specific immune response and its duration, and not the MTD or pharmacokinetics. The

vaccine was very well tolerated, provoking only grade 1 or 2 of adverse events; the MTD was never achieved.
Secondly, after optimizing dose and schedule, a randomized trial was conducted to assess the preliminary efficacy in terms of survival and not response rate. Tumor shrinkage was rarely observed while all vaccinated patients had a trend toward SV benefit that was significant in those patients with 60 years old or younger. The Kaplan Meier survival curve showed a non-proportional hazard ratio, illustrating the delayed (not immediate) effect of the drug. CIMAVax EGF needed at least 3 months to induce a mature, neutralizing immune response and a consequent survival curve separation.
Finally, vaccination was not stopped at the moment of clinically irrelevant, radiologic progression. Patients received chronic vaccination, which increased their probability of becoming good responders and long survivors (González et al, 2011)

Stages of clinical trials typically used for clinical development of new chemotherapeutic drugs	Stages of clinical trials proposed for cancer vaccines development	Evidence Levels	CIMAvax EGF trial number
Phase I trials Phase II trials	PPT	IIa	1
			2
			3
			4
			5
Phase III trials	ET	Ib	6
			7

Table 5. Relation between clinical trials stages and Evidence Levels

7. How to implement the changes in clinical development paradigms for cancer vaccines?

There are clear facts showing that the old paradigms for chemotherapeutics development, no longer apply to cancer vaccines. But paradigms not only differs in contents, but also are the source of methods and normative of solutions accepted by a mature scientific community in a given moment. As a result, receipt of a new paradigm often necessitates a redefinition of the corresponding science.
Moreover, an existing paradigm is shared by members of the scientific community who are engaged with the same. A paradigm shift requires a change not only in tools, but also in the visions of the problem by the related scientific community.
The question is: What is the process by which a new candidate for paradigm replaces its predecessor?
In this case, Axel Hoos et al (Hoos et al, 2007) have firstly described the needs of a paradigm shift for development of cancer vaccines and other related biologics. They have defined new terms or vocabulary according new needs and explained how to apply these new tools in further products development.

Many people working in cancer vaccines development are facing the need of a change in clinical development paradigm as described by Axel Hoos et al and currently been being borne out in practice. As usual in the history of science, crises arise in different places at once, in this case, caused by the emergence of new therapies (cancer vaccines) that do not agree with the mechanism of action of these previously used (cytotoxic antitumor therapies). These people that faced firstly the needs of changes are the pioneers of the new paradigm and have the challenge of ¨converting¨ the rest of the scientific community to the new ideas.
How to induce the conversion and how it resists? Probably the single most common argument put forward by proponents of a new paradigm is that they can solve problems that have led to the old paradigm to crisis. As it has been extensively explained in this chapter, new paradigms proposed for cancer vaccines development solve the problems for which the old paradigms no longer work.
The challenge now is to persuade the whole medical community as well as the Regulatory bodies on the new conceptions, which will result in a more direct development of new drugs and a more rapid availability of the same for patients with cancer.

8. Conclusion: A field of science in transition

As Thomas Kuhn said in his book The Structure of Scientific Revolutions: ¨In science occurs as in manufacturing: a change of tools is an extravagance that is reserved for occasions that demand it. The significance of crises is that they provide an indication that it is time to change tools¨ .This is precisely what is going on in the field of cancer vaccines.
Cancer vaccines are, as other biological molecules, product of the development of Biotechnology, a tool of science which opened a new wave of opportunity for cancer immunotherapy. It created the possibility of finding and manufacturing biological molecules with the same purity, reproducibility and scalability of classic chemical pharmaceuticals. These novel therapeutical tools have the attribute of specificity, which means possibility of therapeutic effect with lack of toxicity. That property makes them very different to the cytotoxic tumor drugs approach for cancer treatment.
Because of that, biotechnology drugs claimed for a change in the paradigm through which antitumor drugs has been up to date investigated, developed, and finally approved. This is especially pertinent in the field of therapeutic cancer vaccines.
We are facing times of changes. As soon as new paradigms are implemented for new drugs development, the faster the profits of these new drugs will be available.
This is just the beginning. Cancer therapy is a field of Science in transition. The changes in the paradigm of product development come together with other changes also intrinsic to novel biotechnology drugs attributes.
There are other important differences between cancer vaccines and cytotoxic antitumor drugs: one is that they are intended to restrain tumor growth, not necessarily to reduce tumor mass, and the second is that they can be used long term.
These features connect with another paradigm shift which is going on in medical oncology, which is the transition of advanced cancer from a rapidly fatal disease into a chronic condition, compatible with years of quality life.
Such a transition is not new in the history of medicine. Diabetes Mellitus Type I was also a rapidly fatal disease until the introduction of Insulin in 1923. Now it is a chronic condition, which cannot be cured, but can be controlled long term.

Biotechnology drugs and specially cancer vaccine have the potential to implement an analogous transition in oncology.

A new paradigm for accelerating the development of cancer vaccines should be embraced by the research community. With these therapeutic tools in hand, also a new paradigm for chronic management of advanced cancer should be embraced by the medical community and by Public Health Systems. Two field of Science which are evolving in parallel, and whose evolutions should merge in the near future, for the benefit of cancer patients and Society at large.

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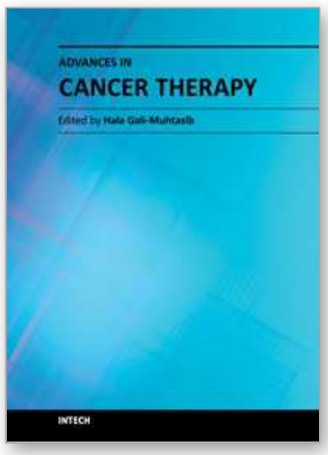

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The book "Advances in Cancer Therapy" is a new addition to the Intech collection of books and aims at providing scientists and clinicians with a comprehensive overview of the state of current knowledge and latest research findings in the area of cancer therapy. For this purpose research articles, clinical investigations and review papers that are thought to improve the readers' understanding of cancer therapy developments and/or to keep them up to date with the most recent advances in this field have been included in this book. With cancer being one of the most serious diseases of our times, I am confident that this book will meet the patients', physicians' and researchers' needs.

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