



CC&C

CELL CONSTRAINT & CANCER

EXECUTIVE SUMMARY

PITCH

Cell Constraint & Cancer SA, France 13280

A disruptive innovation in oncology

• Proof of Concept in 2015: **'Action of Mechanical Cues in vivo on the Growth of Tumor Grafted subcutaneously'** (Published 21 April 2016, PloS One, R. Brossel et al). [Http://dx.doi.org/10.1371/journal.pone.0152885](http://dx.doi.org/10.1371/journal.pone.0152885)

This 'Proof of Concept' in vivo was performed in collaboration with the 'Institut Curie', Paris.

We analyzed the results with Dr. JM Guinebretière (pathologist, Institute Curie): the concept is validated. Indeed, there is a very significant difference in tumor growth between the tumors treated with 'stress field' and control groups in vivo by measuring tumor volume, and ex vivo, on digitized biopsies.

Next step: Proof of Efficacy: 'orthotopic' graft of human pancreatic cancer in a mouse pancreas.

The product, a combination of two medical devices: a magnetic field gradient generator and magnetizable iron nanoparticles. The nanoparticles are located around (not in) the tumor and act as 'BioActuators', transforming magnetic energy into mechanical energy. The therapeutic agent is thus a 'stress field'.

To sum up, Cell Constraint & Cancer (CC & C) is a Medtech engaged in a new approach to cancer research. Our disruptive innovation (PCT WO 2015 004 285) involves the application of mechanical signals (constraint / stress field) in the treatment of cancer.

This new approach to cancer radically changes our views on tumor development and possible therapeutic solutions.

CC & C is protected and has an innovative approach.

Today we propose an experimental follow up: get to show action on human pancreas cancer tissue grafted in mouse pancreas. Obtaining this 'Proof of Efficacy' in vivo open perspectives in the treatment of tumors for which current therapies are insufficient, as locally advanced pancreatic cancer, unresectable. This would be the first therapeutic application of 'Physical Oncology', defined as the study of cancerous tissue with the tools of physics of mechanics.

Demonstration of Proof of Efficacy of our process allows for consider a switch to man in 2021. We have already started a biological and physical feasibility study of the Proof of Efficacy planned in 2018.

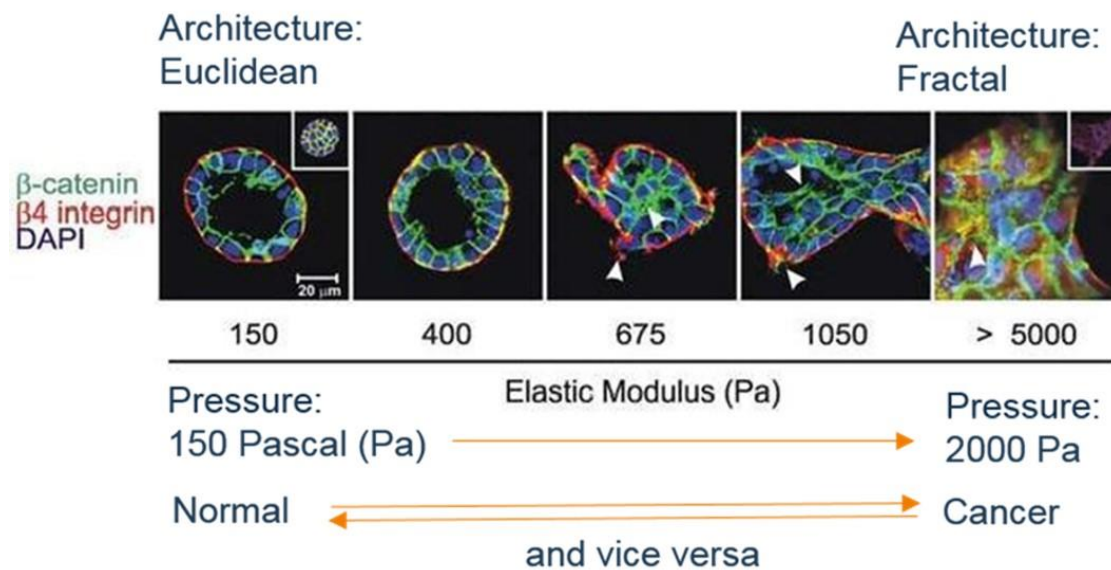
SCIENTIFIC ISSUES

'Physical Oncology' is poorly represented in Europe, but very active in the United States where it was born (see Office for Physical Sciences and Oncology, NCI, <http://www.physics.cancer.gov/> and Asia (Institute of Mechanobiology, Singapore) <http://www.mbi.nus.edu.sg>).

Our patent protects the ability to apply a constraint to a tissue *in vivo*. To do this, we are positioning the magnetizable nanoparticles around tumors and then apply a gradient magnetic field to the tumor via the nanoparticles from the outside. Nanoparticles are vectorized on integrin alpha v beta 3 overexpressed in tumor neovasculature. This results in a constraint applied to the tumor, which induces genetic and epigenetic modifications and remodeling of architecture that restores the normality of the appearance under the microscope and the cellular function of the tumor. This was amply demonstrated *in vitro* in culture of tumors in 3 dimensions (M Paszek 2005, F Montel 2011, M Olcum 2014 and others...).

The first article: Paszek MJ, *et al.* (last author Valerie Weaver) (2005) Tensional homeostasis and the malignant phenotype. *Cancer Cell* 8(3):241-254

Figure 1



(With permission of M.Paszek)

The only modified parameter is the pressure around an acinus (elementary unit of milk secretion) of the human mammary gland cultured in 3 dimensions. This increase in surface tension, from 150 to > 5000 Pascal, is accompanied by architectural and biological changes.

From left to right, the initially Euclidean (normal) architecture becomes fractal (cancerous).

From left to right, we see activated proteins that accompany the cancerous transformation. This phenomenon is reversible.

Our patent PCT / WO 2015/004285 protects the ability to apply stress to tissue *in vivo*. To do this, we position magnetizable nanoparticles around tumors and then apply a magnetic field gradient to the tumor via a magnet, from the outside. Nanoparticles are vectorized on alpha v beta 3 integrins overexpressed in tumor neovessels. This results in a constraint applied to the tumor: in fact, the nanoparticles act as "Bioactuators" transforming magnetic energy that comes from the outer magnets into mechanical energy directed towards the tumor. The possibility of

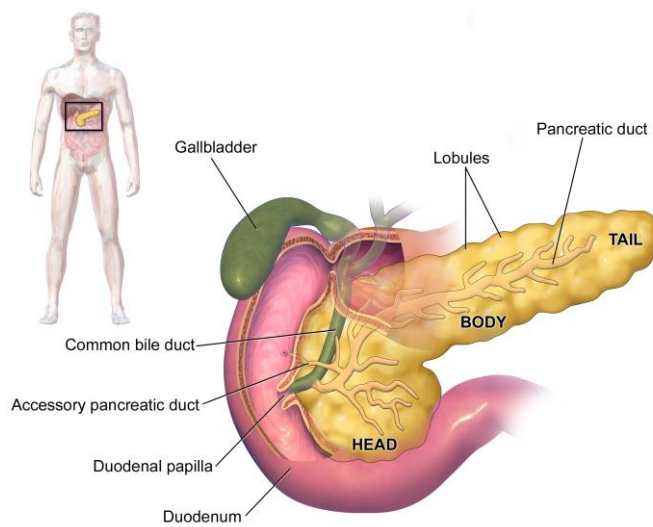
acting on a tumor using stress has been widely demonstrated in vitro in 3-dimensional tumor culture (M Paszek 2005, F Montel 2011, M Olcum 2014 and others).

Our innovation relates to the portability of in vitro 3D (tissue culture in 3 Dimensions) to the in vivo. In other words, Paszek, Montel and others have shown the ability to act on a cancer tumor, but only in vitro; CC & C applies the same principles (application of a constraint / stress field in cancer tissue), but in vivo in animal.

MEDICAL NEEDS

The pancreas is an organ located deep in the abdomen.

Figure 2: the pancreas in the human body



Pancreatic cancer is a malignant tumor whose prognosis is generally poor. The chances of survival at 5 years range from 5% for inoperable cancers, to 30% when the tumor could be operated when discovering.

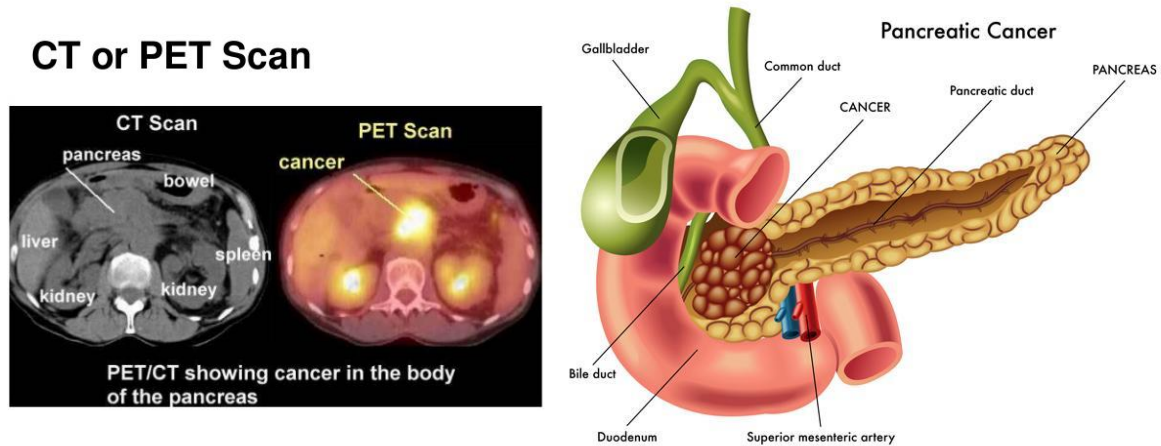
In the US, pancreatic cancer causes about 42,000 deaths annually. On average, 50,000 new cases are diagnosed each year and this figure is increasing year by year.

The diagnosis of pancreatic cancer is most often carried out at a late stage of the disease, which is why the 5-year survival is only about 5% on average.

In the world there are 400,000 new cases of pancreatic cancer per year; 40 % are locally advanced, non-metastatic, unresectable.

In 2016, more patients died of pancreatic cancer than of breast cancer.

Figure 3: pancreatic cancer



A CT Scan (left) and a PET Scan (right) showing a pancreatic cancer.

There is no known cause to pancreatic cancer, although it is more common in patients with chronic pancreatitis (inflammation of the pancreas).

Surgery is the standard treatment, the only cure, if the patient's condition allows. This is a heavy and difficult operation.

The resectable patients at the outset are only a minority, 10%, and a majority of them will relapse.

Chemotherapy, until recently, was only palliative. The recent introduction of the protocol 'Folfirinox' (in US often Abraxane® gemcitabine), association of 3 chemotherapies, helped make operable inoperable tumors at the outset and significantly increases survival in palliative treatment. But this protocol, very heavy, is applicable only to a minority of patients.

Immunotherapy is a real and exciting innovation. It is at its beginning and in the pancreas, it is not yet discern its possible applications, except for a very small minority of so-called 'patients with microsatellite instability'.

Pancreatic cancer treatment is, whatever the technique used, a cumbersome process, complex and uncertain.

Faced with existing treatments, Cell Constraint & Cancer offers a new approach to pancreatic cancer treatment using mechanical signals and not biological signals (molecule, drug, immunology).

FINANCIAL REQUIREMENTS

For the current year, we hope to raise about \$ 500,000 to complete the Proof of Efficacy. We expect the first benefits from the fourth year. In fact, our product is not 'early': the therapeutic action is based on the laws of physics; accordingly, it is quantitative (as opposed to products based on the laws of biology) can be modeled and can be predictive (as opposed to products based on the laws of biology); development may be partly parallel and not sequential. In addition, for the same reasons, there is much less biological hazard.

Very similar nanoparticles and magnetic field gradients were used for decades on patients without significant toxicity.

We will need \$ 5,000,000 for the human prototype, to arrive at a clinical trial Phase I / IIa in patients with pancreatic cancer 'unresectable, non-metastatic'.

INDUSTRIAL PARTNERS

The aim is to engage after the Proof of Efficacy a collaboration with an industrial firm mastering the technique of superconducting magnets and the sale of heavy equipment to hospitals. After a common development including deliverables, time-lines, Go / No Go, etc. we will continue to work with this company.

In fact, our product is not 'early': the therapeutic action is based on the laws of physics; as a result, it is quantitative (unlike products based on the laws of biology), can be modeled and can be predictive (unlike products based on the laws of biology); likewise the development can be partly 'parallel' and non-sequential. In addition, for the same reasons, there is practically no "biological hazard" that stops the development of 90% of the molecules, and the probability of abandonment of the product under development by toxicity or inefficiency is much lower than for a drug, a molecule or a biological process.

Very similar nanoparticles as well as magnetic field gradients have been used for decades in patients without significant toxicity.

We will need a human prototype to reach a Phase I / IIa clinical study in patients with non-operable, non-metastatic pancreatic cancer. The total cost of development to reach the market, is estimated at 5 M €.

THE COMPANY

CC & C



Mr. Barthélémy Brossel, CEO, PR, Social Network and Communication



Mr. Rémy Brossel, CSO, MD, Medical Oncologist, Physicist

They are helped by a team: assistant: Christine Grau and Scientific Board composed of mathematicians, physicists, oncologists and entrepreneur in Health Facilities:

Daniel Gabay
Mathematician (Polytechnic, Paris)

Stéphane David
Industrial manager (PhD, CEA)
Specialist in magnetism

Christian Chillet
Researcher (PhD, CNRS / G2ELab)
Specialist in magnetism

Eric Peltier
MD, CEO Novacyt
Medical device development specialist

Roy Weiner
MD, Oncologist (Ass. Dean, Tulane University, US-LA)

CELL CONSTRAINT & CANCER SA, founded in 2009, is a French company with a capital of € 383 025 governed by the laws and regulations in force.

Postal Address:

Le Mas l'Hermitte 331 chemin de la poterie
F13280 Raphèle-les-Arles, France

Phone: +33 (0) 6 738 769 87 - email: brossel.remy@gmail.com

Website: <http://www.cellconstraintcancer.com> LinkedIn : <https://fr.linkedin.com/in/remybrossel>

CELL CONSTRAINT & CANCER SA belongs to private individuals.

The company is registered in the commercial register in Tarascon under number:

RCS 511-620-890 Tarascon

Creation date: 13 March 2009

The share capital is divided into 76,605 shares with a nominal value of € 5 each, fully paid.

TO WHOM?

Our first indication: locally advanced pancreatic adenocarcinoma (40% of pancreatic cancers):

Some data:

In the world, there are 400,000 new cases of pancreatic cancer per year and 350,000 deaths; 40 % are locally advanced, non-metastatic, unresectable.

It is a cancer on the rise; now the fourth leading cause of cancer death and the second in 2030 if nothing is done.

This is an obvious 'unmet need' and a public health problem.

Obtaining an indication is done through a clinical study. The first clinical study is planned in the pancreatic cancer non-metastatic locally advanced, to make cancer resectable.

This Ph I / IIa study is short and requires few patients.

Treatment:

This is a local treatment.

Intuitively, one can imagine a treatment 'radiotherapy-like', similar to radiotherapy but with an intravenous injection of nanoparticles before putting the patient on the treatment bed.

Figure 4



Turnover:

A machine of this type could have a price similar to MRI.

Consumables (nanoparticles vectorized to integrin alpha v beta 3 overexpressed in neovascularization) will be sold over \$ 3,000, with a significant margin.

Development Strategy of Indications:

It concerns first cancer with few resources of treatment such as the pancreas and without development of new treatments (such as targeted therapies, immunotherapy) perceivable in the coming years.

Immunotherapy is still in a research phase and may be the only indirect competition, but probably synergistic. At present the only indication of immunotherapy is experimental: pancreatic cancer with microsatellite instability, a rare phenotype.

But, more importantly, immunotherapy is the first treatment of cancer that takes in account the importance of the dialogue between the ‘environment’ of the cancer (the ExtraCellular Matrix) and the cancer tissue itself.

The pattern ‘no foreseeable major innovation; locally advanced cancer’ may be declined on many locations: biliary tract, primary liver cancer, glioblastoma (brain), uterus etc. In total, there are perhaps a quarter of a million new patients in the US who may be affected each year.

The installation of this type of machine (‘practice – changing’), country by country takes time (authorization, environment, staff training, etc.), but growth is rapid, as shown by the MRI system in the 80s and close to us Pet Scan.

COMPETITION

There is no direct competition in vivo. The methods used in vitro by Mr. Paszek (increase of the surface tension), or by F. Montel (increase in the osmotic pressure), etc., cannot be used in vivo.

The mechanical characterization of Circulating Tumor Cells is another application of Physical Oncology.

THE ONCOLOGIC CONTEXT

Current innovative drug treatments -targeted therapies- develop slowly after the only first two spectacular results (imatinib, trastuzumab...). Current publications of academic or industrial origin offer interesting but modest improvements at a huge price. Our treatment is compatible with the addition of a mode of therapeutic action in principle independent of actions on the transduction-transcriptional and signaling cascades. Eventually, very few patients are cured by targeted therapies (CML, adjuvant HER2 breast cancer).

Immunotherapy has, for now, significant limitations: few sensitive patients, relapses, significant toxicities.

STATE OF THE ART OF INSTRUMENT AND VECTORIZED NANOPARTICLES

The technique of magnetic fields is a science of the engineer mastered for long time. Magnetic Particles Imaging uses large gradients very well tolerated by animals.

The transition from animal to human prototype requires the use of superconducting magnets.

The proposed device is close to a MRI / NMR in the design, volume and cost of production. Budgets are difficult to assess today, as well as development time. However, and as a first approximation, we can consider that it will take two years to get a prototype to the dimensions of a patient.

An intermediate step is the construction of a model for rodents, used in the 'Proof of Efficacy', which will work on electromagnets, without drastic cooling, will modulate the amplitude and frequency and will begin the fields to work over distances in centimeters, so extrapolable to humans.

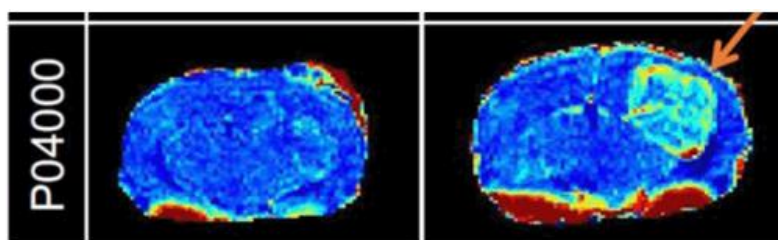
Feasibility studies on this device were presented at the American Association for Cancer Research in Boston in June 2016 (First meeting AACR devoted to 'Engineering of Physics of cancer').

<http://actucancerpancreas.blogspot.fr/2016/05/abstract-qui-sera-presente-par-remy.html>

An equipment for use in animals is being built in Grenoble, France.

Nanoparticles very similar to our product already exist. Designed to image neovascularization around the tumor, they allow to deposit a substantial amount of iron around the tumor itself. But these ferric nanoparticles used as MRI contrast agents have been a commercial failure and development was stopped. They are available for use in animals.

Figure 5



Anti-angiogenic treatment follow-up

R2* maps in a U87-bearing mouse model: specificity of P04000 as an $\alpha v\beta 3$ -specific imaging biomarker of angiogenesis.

These contrast agents have gone through preclinical procedure and therefore have a pharmaceutical file according to pharmaco-toxicological and clinical standards of the FDA and the EMA in Europe. Clinical toxicity is extremely modest, especially intravenously.

Our goal is to reach 6T/m at the Extra Cellular Matrix / Tumor interface.

The equation describing the applied pressure is linear.

DEVELOPMENT STRATEGY

We believe that the last step of research is the Proof of Efficacy in vivo followed by the publication of an article in a scientific journal. The next step -development- is working with industrial to manufacture the human prototype and experimental batches of nanoparticles.

This will be followed by the pre-clinical development: toxicology, CE Mark / PMA and clinical phase I / IIa embedded.

To raise funds, private saving is not enough. Indeed, a start-up that develops a disruptive innovation has reduced access to public support and is too risky for investment funds.

We are currently looking for investors and industrial partners.

As far as animal experimentation (Proof of Efficacy) is concerned, we are engaged in two collaborations:

- Stanford University, Ca
- Faculty of Medicine Bichat, Paris

Barthélemy Brossel

CEO

November 21th, 2017

+336 738 769 87

www.cellconstraintcancer.com

CC & C SA
Le Mas l'Hermite
331 Chemin de la Poterie
F13280 Raphèle-les-Arles
France