# Bio-Modeling Systems

## The Mechanisms-Based Medicine Company

Targeted cancer therapies issues and what could be done.

BMSystems' cancer CADI programs and novel strategy proposal

## European Cancer Conference 2012

Hamburg november 14, 2012 updated

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*Extract of the Presentation and incorporation of additional slides*

***This is not the pitch presentation***

***This document is for download only***

*We added necessary details and explanations in the slides to help the reader*

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# F: The Individualized Oncology Therapy Issues

## The Individualized therapy mirage vs. novel concept & multi-therapies

Request: Targeted treatment does nothing more than selecting resistant cancer cells;
What alternative solutions could be proposed (full presentation available)

### CADI™ past programs

F1-2003, CANCER THERAPEUTIC STRATEGY: Integrated transcriptome analysis of the cellular mechanisms associated with Ha-ras-dependent malignant transformation of the human breast epithelial MCF7 cell line. Nucleic Acids Research. Collaboration with INSERM unit 553. Publication

- Outputs: Identification of 4 differentialy deregulated pathways in malignant cells. Test of a combination of 3 drugs, never used in oncology, that showed synergistic apoptotic activity in-vitro in malignant cells only. Additional outputs: anti-farnesylase can't work!

F2-2004, CANCER METASTASIS MECHANISM : Mechanisms targeted by the ADAM-15 RDG peptide to induce cytostasis in very aggressive breast cancer cells in vitro (MDA-MB 231)and in vivo. Collaboration with INSERM unit 553.

- Outputs: Identification of the ADAM-15RGD mechanism of action and the limits of its therapeutic application. The mechanism is used for normal tissue repair and can't be blocked without dramatic consequences.

F3-2005, UNDERSTANDING OF TAMOXIFEN RESITANCE (CANCER) : Integrative analysis of gene expression patterns predicts specific modulations of defined cell functions by estrogen and Tamoxifen in MCF7 breast cancer cells. Journal of molecular Endocrinology. Collaboration with INSERM unit 553. Publication

- Outputs: explanation for the relapse mechanism: "antibiotic resistance-like" form of selection mechanism identified.

*These three programs show that the interpretation of cancer as a chronic disease raises numerous long term efficacy issues due to the "antibiotic resistance-like" behavior of tumor cells.*

*Poor efficacy and too high prices of treatments only reinforce payers reluctance to reimburse them. Based on HIV experience, a new paradigm, simultaneously addressing different targets combined with a novel metastasis control strategy, must be investigated.*

A tumor is rarely composed of one type of malignant cells. BMSystems, through his 3 programs, identified the narrow limits of mono-targeted therapies and proposes a new approach to oncology, based on a therapeutic strategy that does not only target the tumor itself but uses the possibilities of surrounding tissue to control metastatic processes while starving cancer cells.



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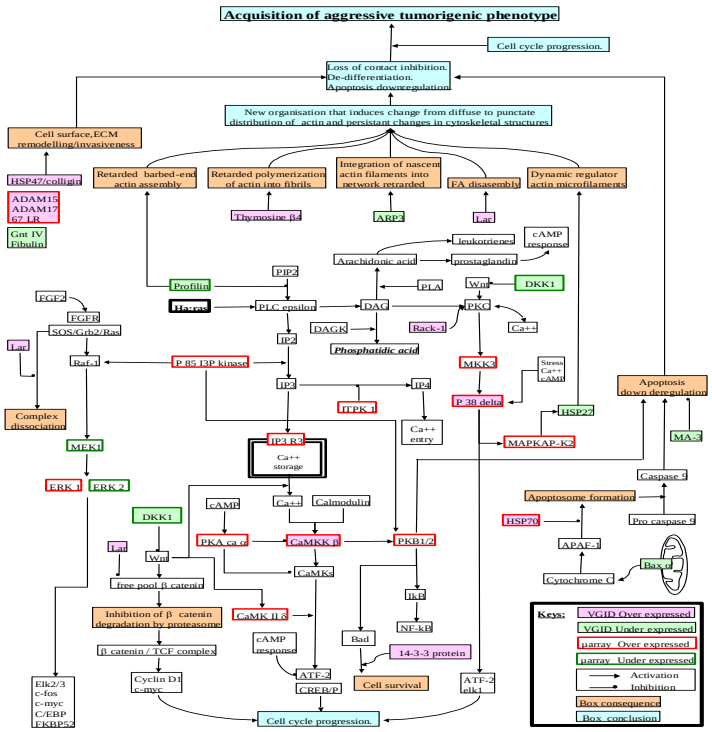
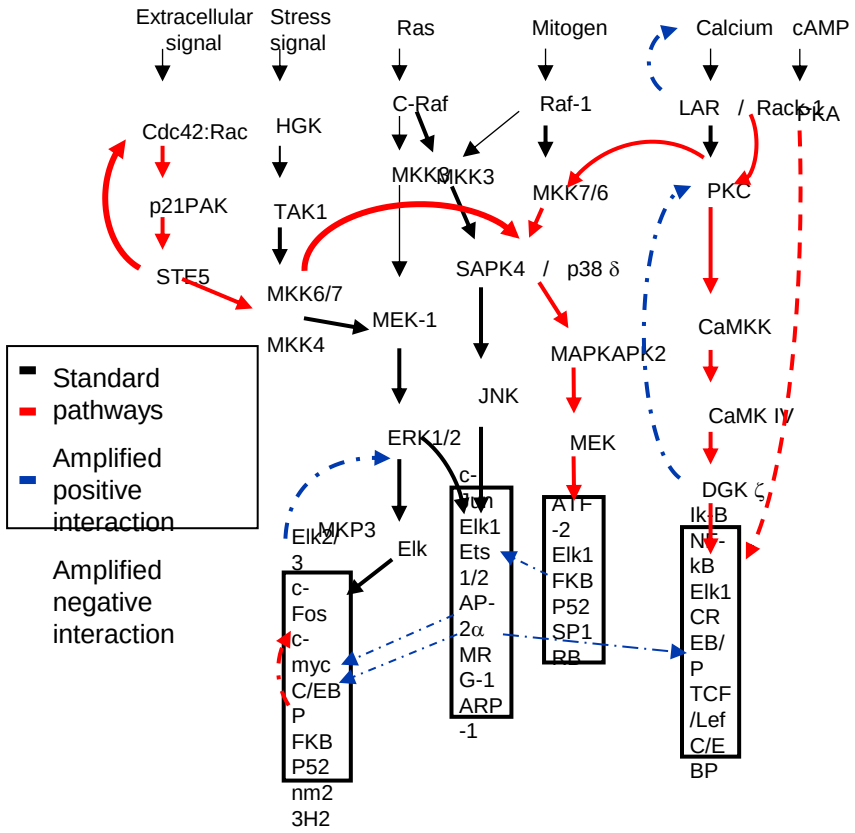
# F1: CADI™ Ras-dependent breast cancer model

1-Ras-dependent breast cancer
Breast Cancer Progression: Cellular Mechanisms Model



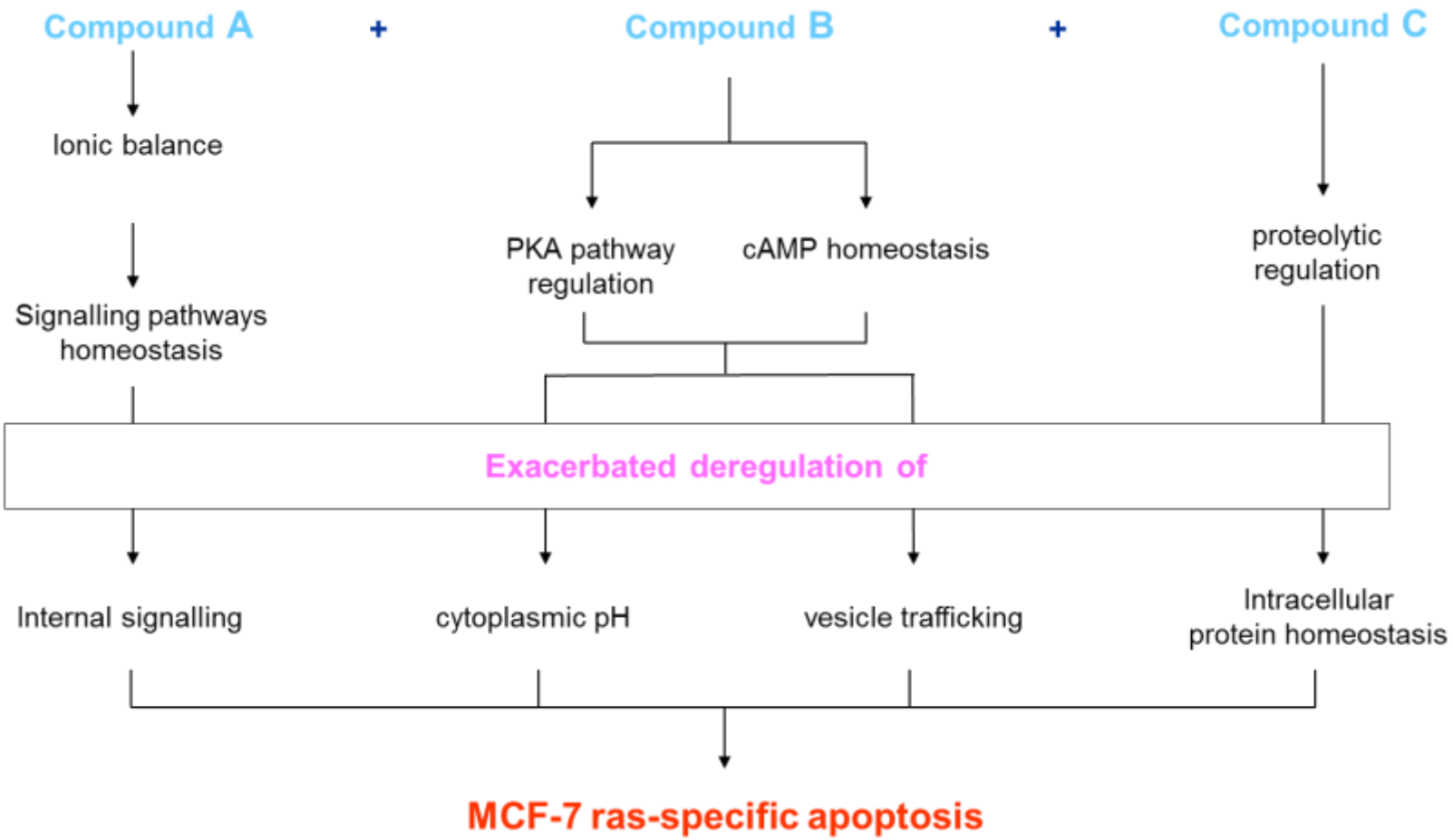

Published in: *Nucleic Acids Research*, 2003, Vol. 31, No. 19: 5789-5804

## CADI™ model extract




Identification of 4 differently deregulated pathways in malignant.
Additional outputs: anti-farnesylase can't work!

# F1: Anti MCF-7 ras intervention using sub-optimal doses (nM)



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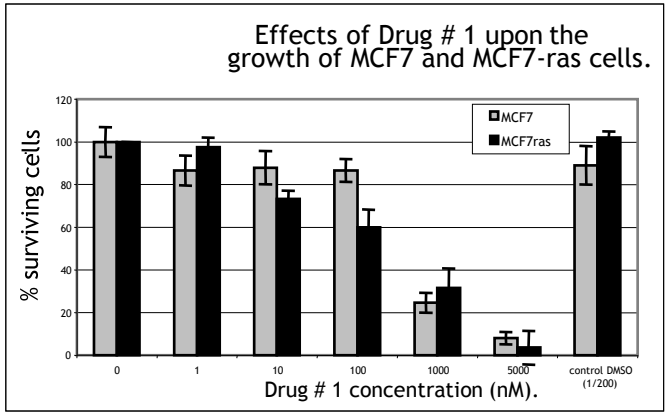
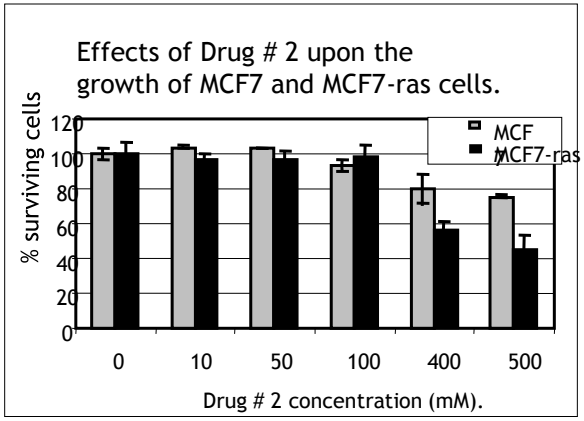
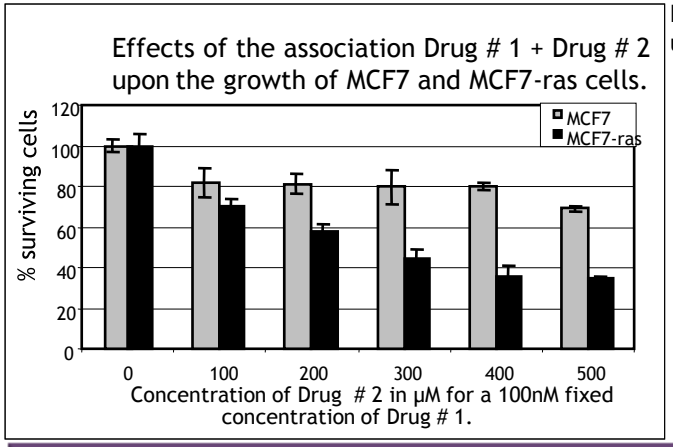
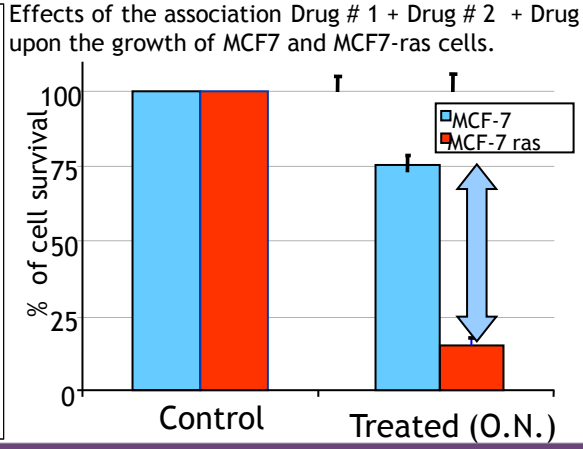
# F1: CADI™ Ras-dependent breast cancer




Biological Validation.
A significant difference when the three compounds, NEVER USED IN ONCOLOGY, are concurrently used.




Test of a combination of 3 drugs, never used in oncology, that showed synergistic apoptotic activity in-vitro in malignant cells only.
This is not a treatment, but this gives novel hypotheses

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# F2: CADI™ Cancer Metastasis

## ADAM-15 RGD peptide mechanisms model

- *10 amino acids fragment (GCGGRGDGGC) derived from the metaloprotease Adam 15.*
- *Induces cytostasis (dormancy) in very aggressive metastatic breast cancer cells both in vitro and in vivo.*
- *The target of this peptide appears to be integrin-containing structures (cell adhesion) but not integrins alone (anti-integrins antibodies have no such effects).*

  - What is (are) the target (s) of this peptide?
  - What mechanisms does if affect? and
  - Why does it induce cytostasis?

- *This model addresses the mode of action of a potential treatment.*

**Collaboration BMSystems-INSERM U 553** (Hôpital St Louis)

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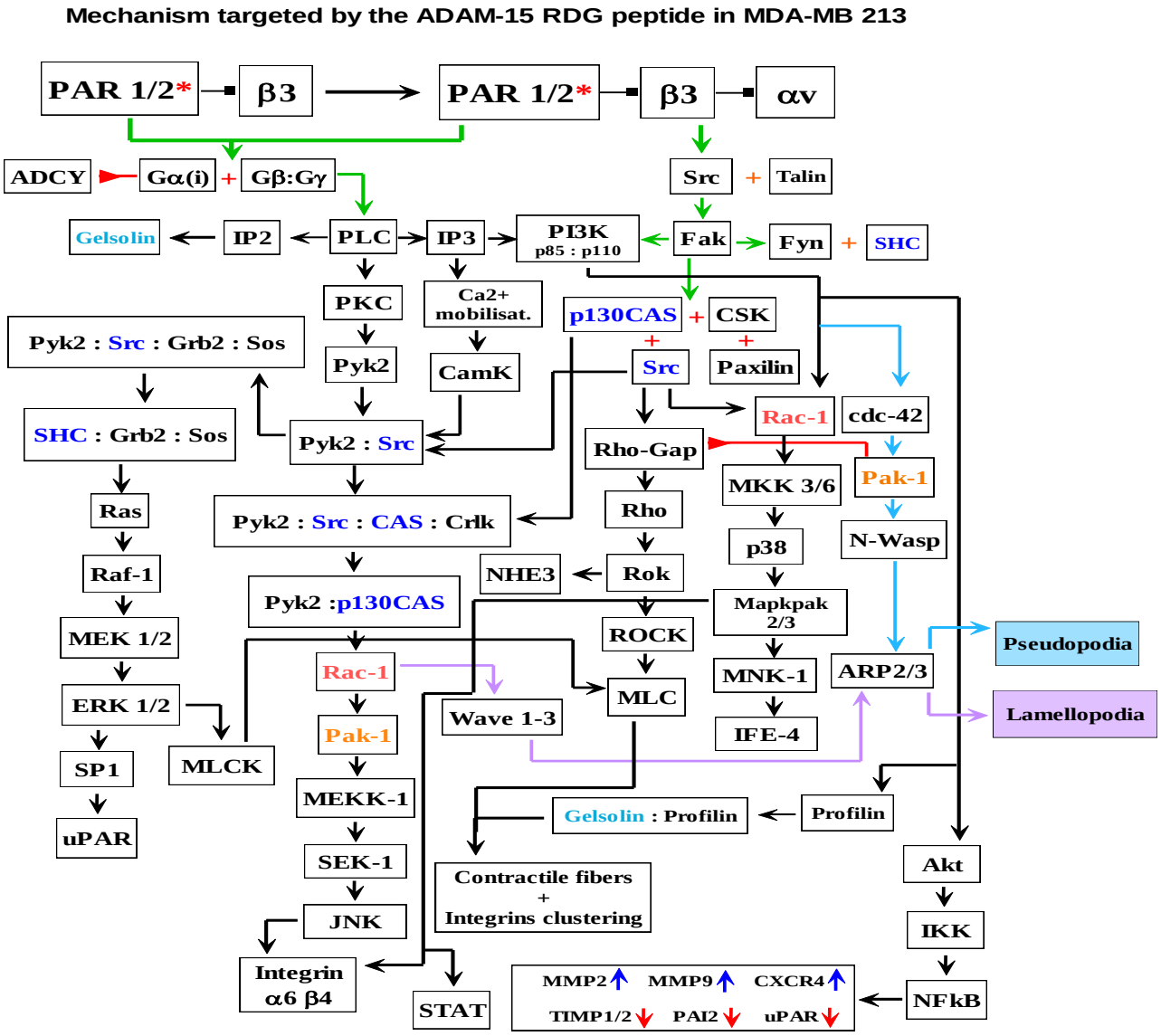
# F2: CADI™ Cancer Metastasis

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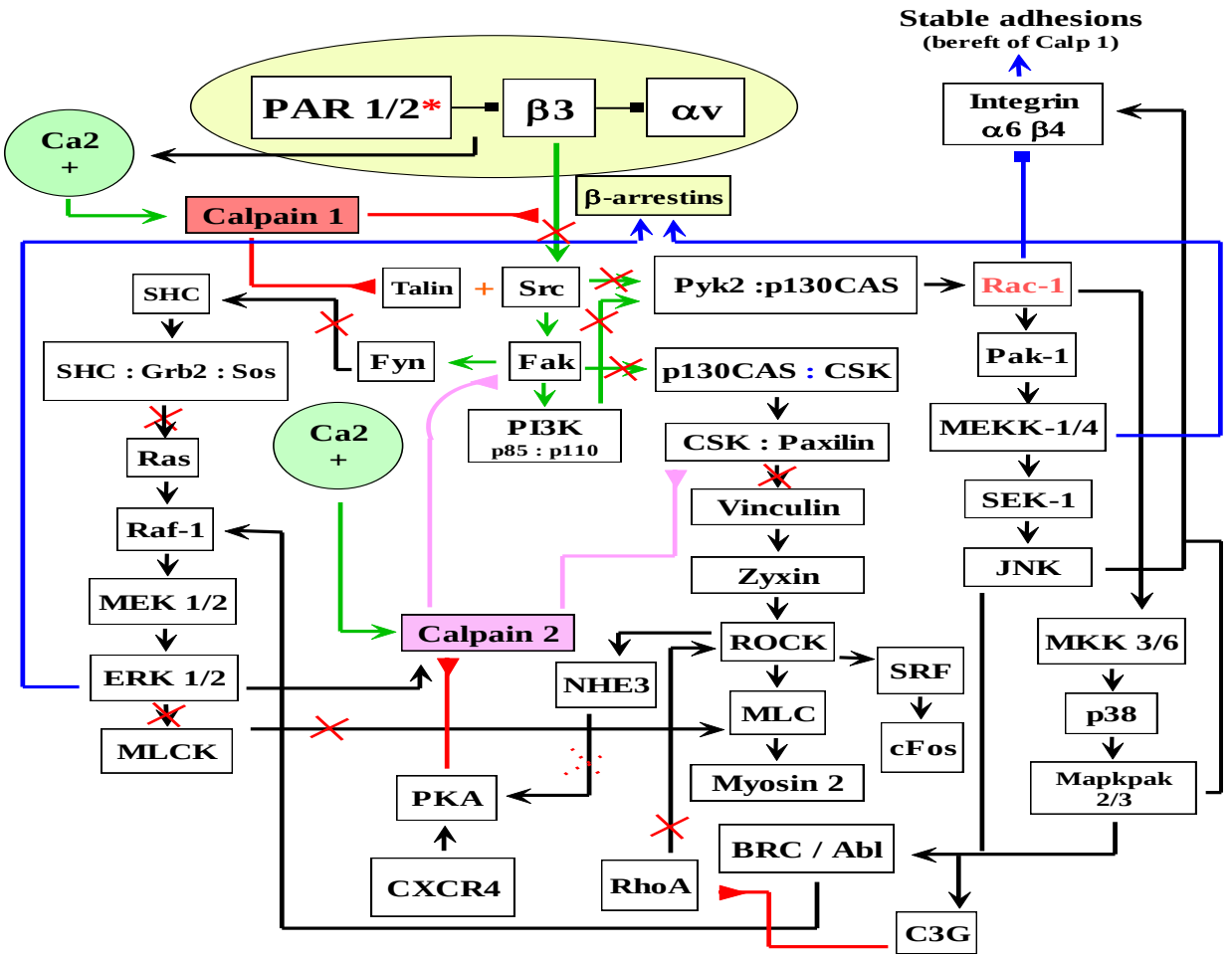
# F2: CADI™ Cancer Metastasis

## Consequences of ADAM-15 RDG peptide binging

### β-arrestins-mediated endocytosis of PAR : Integrin complexes & cytoplasmic segregation of ERKs & MEKKs 1/4

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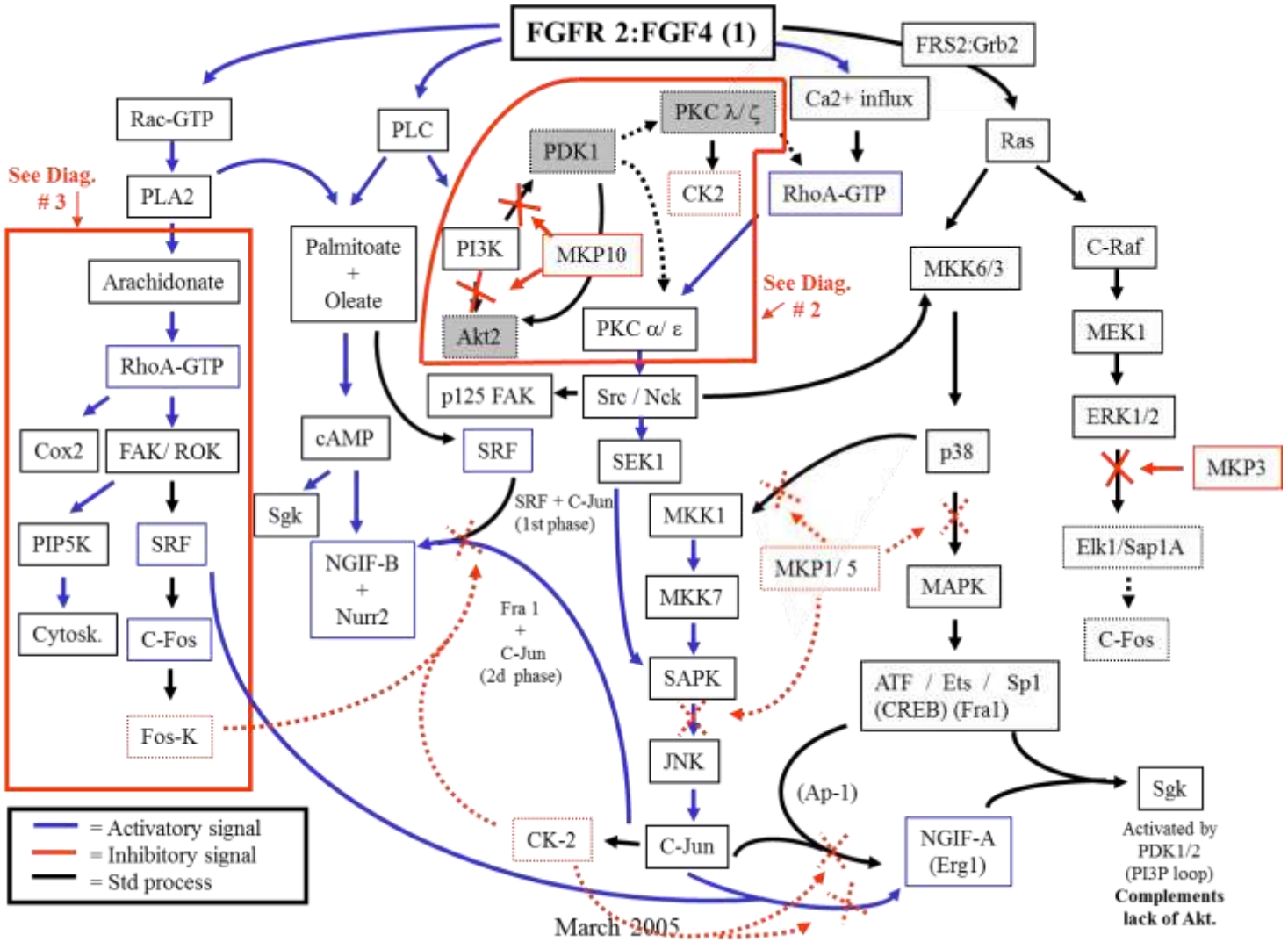
# F2: CADI™ Cancer Metastasis



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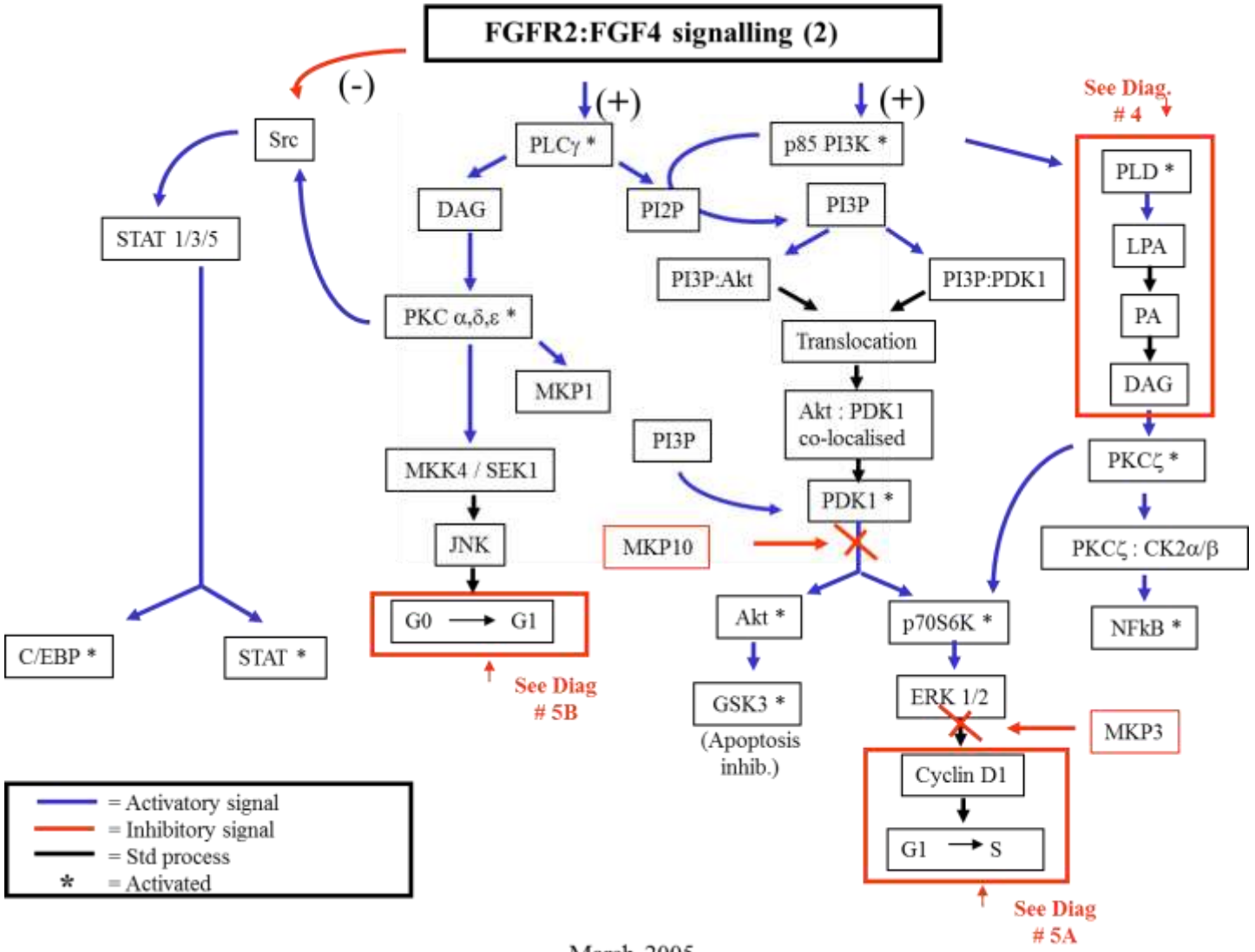
# F2: CADI™ Cancer Metastasis



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# F2: CADI™ Metastasis: Practical outcome.

- Treatment with the ADAM-15 RGD peptide massively triggers the integrins-associated, β-arrestin-dependent endocytotic mechanisms.
- This effectively abolishes integrins-dependent cytokinesis mechanisms while inducing cytostasis in cells where these mechanisms are being implemented.
- But this does NOT solely address metastasis, where integrin-dependent mechanisms are inappropriately activated.
- It will also address and inhibit physiologically coherent integrins-dependent cytokinesis mechanisms, such as fibroblasts migration during wound healing, or repair of damaged capillaries.
- Thus, the potential therapeutic benefits of ADAM-15 RGD (inhibition of integrin-dependent metastasis) are annihilated by direct, highly undesirable effects (failure of wound healing and thus serious risks of gangrene; failure of vascular repair and thus serious risks of multiple organ failures; etc.).

In spite of high efficacy, the therapeutic potential of the ADAM-15 RGD peptide is extremely low.

→ ***Reconsider therapeutic development.***

Ouputs: The mechanism is used for normal tissue repair and can't be blocked without dramatic consequences.

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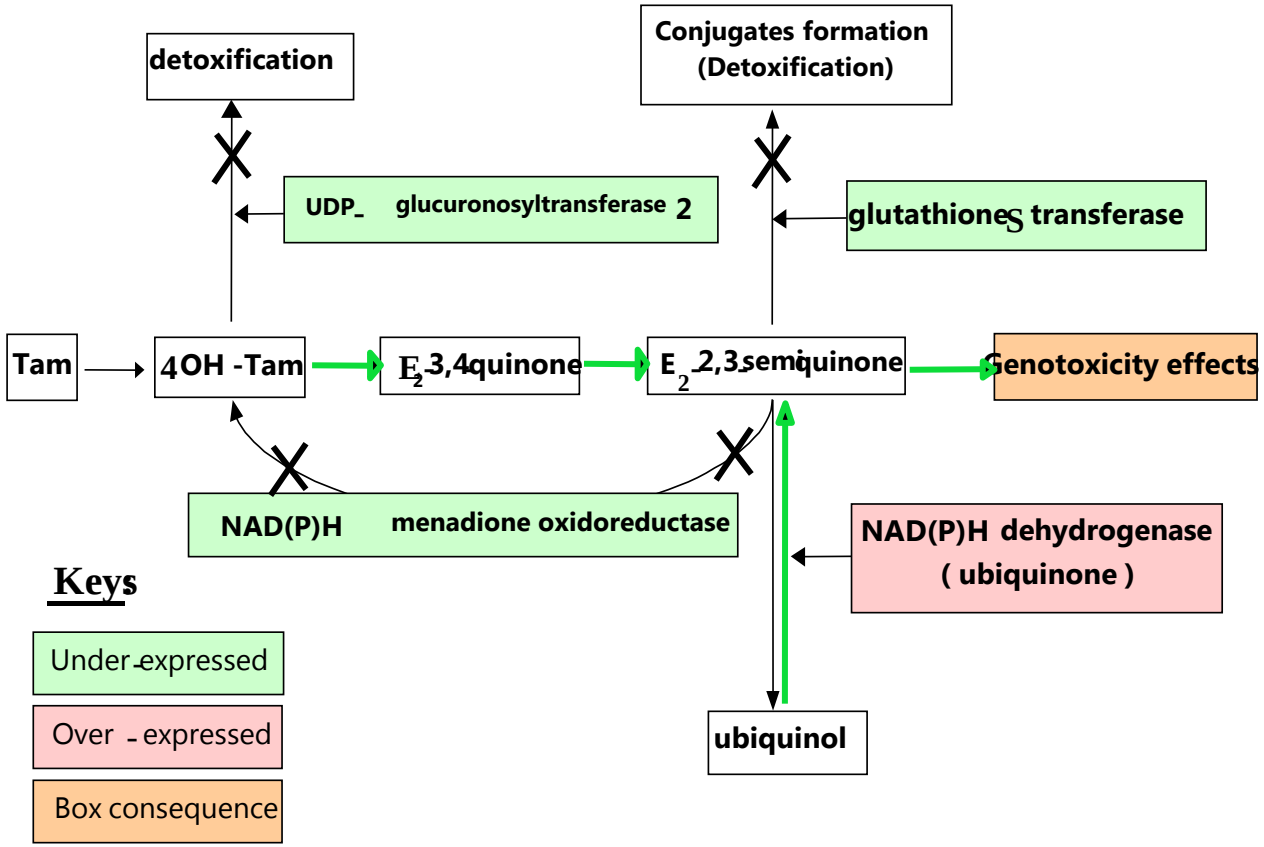
# F3: CADI™ tamoxifen-resistance model.

## Validation:

**RNA-chip technology (9 independent assays) + Enzyme activity assays.**

**Induction of Quinone-resistance**




F. Gadal *etal*. *J. Molecular Endocrinology*, 2005, Vol.34, 61-75.

March 2005

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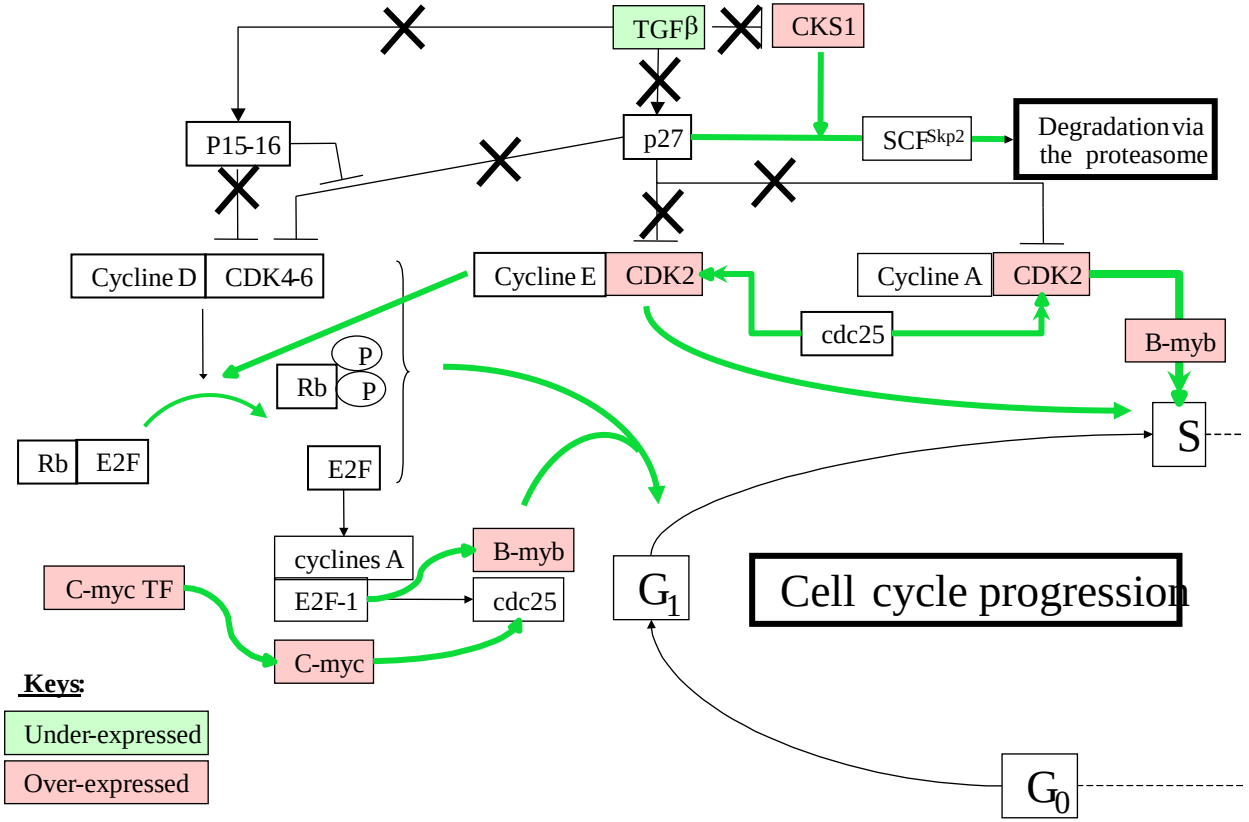
# F3: CADI™ tamoxifen-resistance model.

## Validation:

**RNA-chip technology (9 independent assays) + Enzyme activity assays.**

**Quinone-mediated suppression of negative feed-back on cell-cycle control mechanisms.**




F. Gadal *etal.* *J. Molecular Endocrinology*, 2005, Vol.34, 61-75.

Outputs: explanation for the relapse mechanism: "antibiotic resistance-like" form of selection mechanism identified

2005

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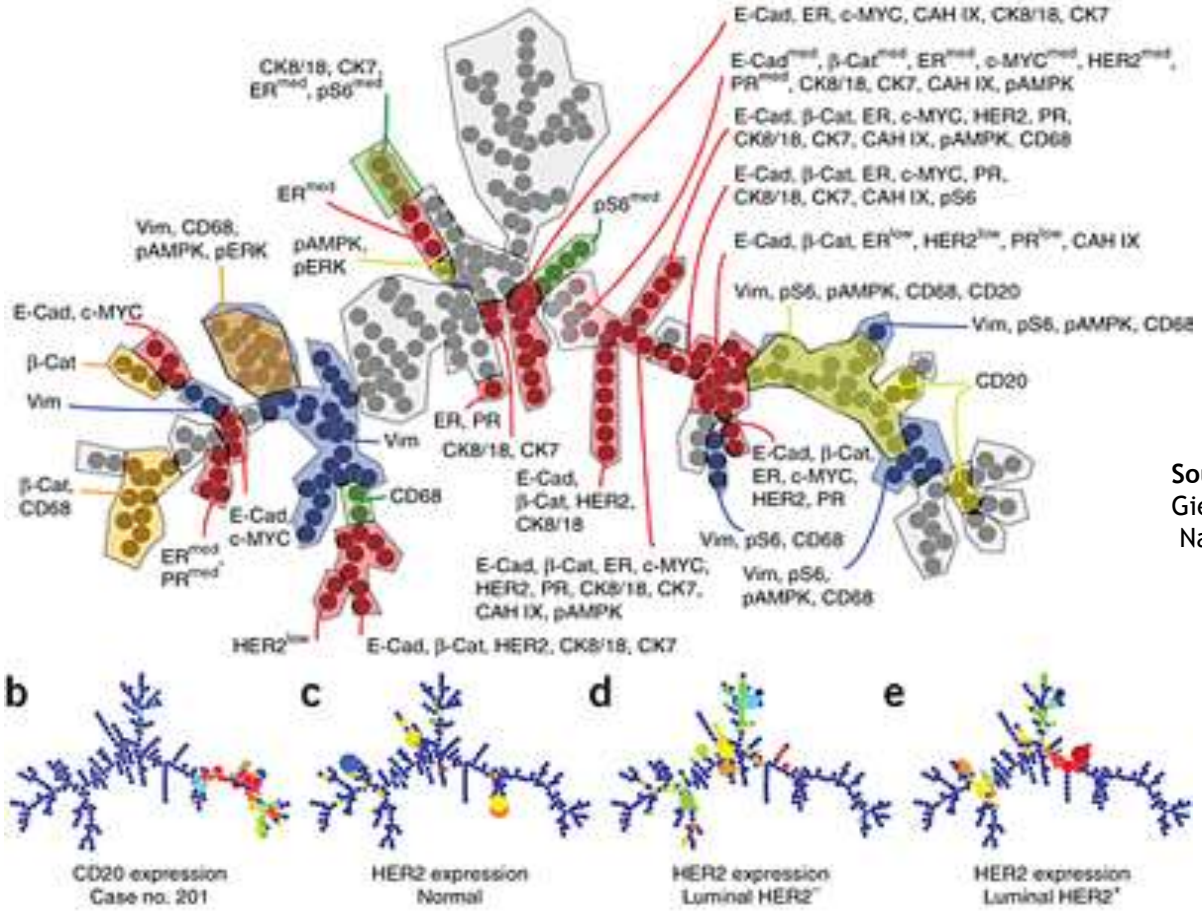
# F4: Precision medicine applied to cancer issues

## 1-Cancer: multiple types of cancer cells within the same tumour




**Source:**
Giesen C. et al. 2014
Nature Methods
doi:10.1038/nmeth.2869



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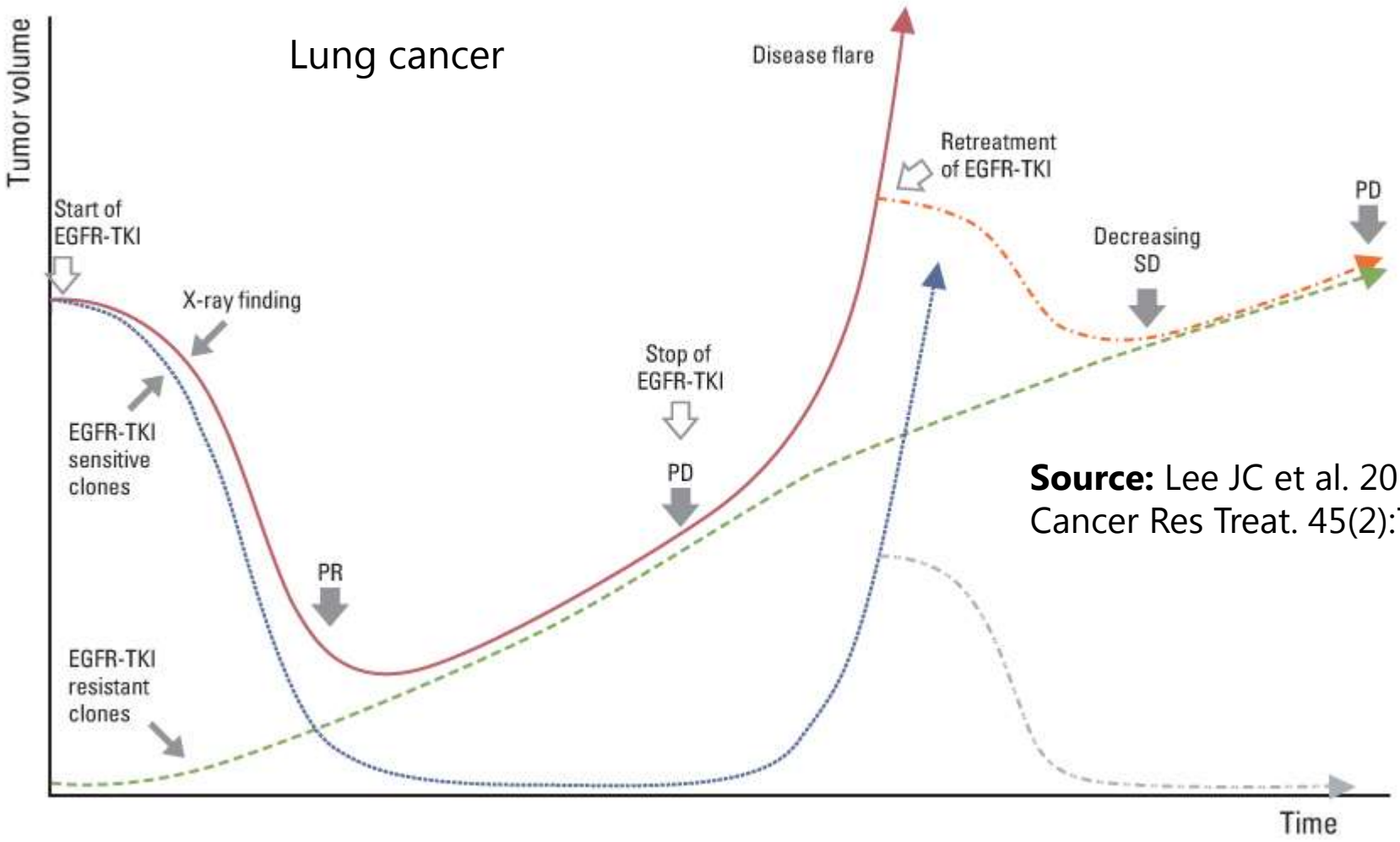
# 2-F4: Targeted treatment does nothing more than selecting resistant cancer cells: The cancer first diminishes & then starts again and cannot be stopped.




**Source:** Lee JC et al. 2013 Cancer Res Treat. 45(2):79-85.



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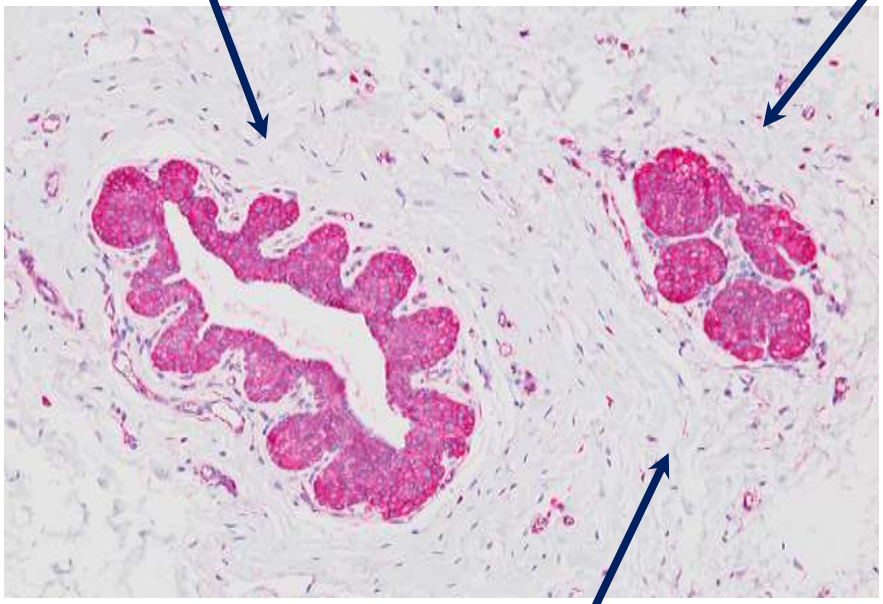
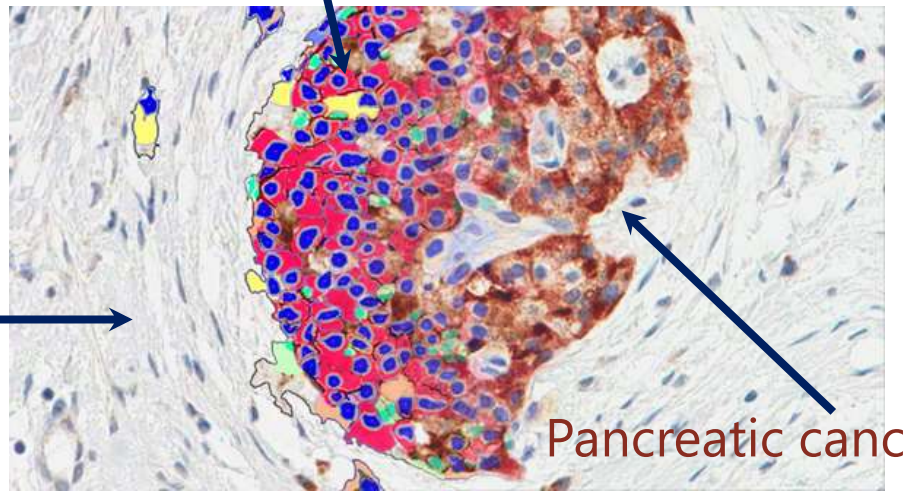
# F4: A novel approach to cancer therapy.

Ductal breast cancer

Non-ductal cancer off-shoot



Multiple types of cancer cells within the same tumour
(each colour indicates a different type of cancer cell)



Pancreatic cancer

**Complementary therapy:**
Peri-tumoural tissue could be induced to "encyst" the tumour, preventing metastases while starving the cancer cells.

Source: http://flagshipbio.com/pancreatic-cancer-drug-development/

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# F4: A novel approach to cancer therapy

## CANCER MESTASTASIS CONTROL PROGRAM:

### Concept

Complementary therapy: Peri-tumoural tissue could be induced to "encyst" the tumor, preventing metastases while starving the cancer cells.

We propose to investigate the "grey zone" between tumor boundary and so-called healthy tissue.

- Objective: To develop a therapeutic strategy that does not target the tumor but the possibilities of surrounding tissue to control metastatic processes.
- I.P. competitive advantage: The possible mechanisms and corresponding therapeutic strategies that will be discovered (surely never used to treat cancers) should be patentable.

### Work done and to be done

- Feasibility Study completed
- CADI v0 to be initiated
- Search for partners for future validation phases



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# BMSystems' CADI™ publications to date

## CADI™ Models published in prestigious peer-reviewed journals: (click on the blue links to get the pdf)

- 2014: CNS Psychiatry publication: American Journal of Psychiatry and Neuroscience. Second publications with the Max Planck Institute of Psychiatry in Munich: Differential proteomics analyses reveal anxiety-associated molecular and cellular mechanisms in cingulate cortex synapses. The first output of the DECIUS CNS research program.
- 2012, CNS NEURODEGENERATIVE & PSYCHIATRY: PharmacoPsychiatry publishes the first review describing a productive vision of Systems Medicine that will change R&D organization and interactions between clinicians & researchers & reveals how the world's first explanation of the mechanisms of the Creutzfeldt-Jakob disease led to the discovery of a truly innovative psychiatric treatment.
- 2011, CNS PSYCHIATRY: Pharmaco Psychiatry publication: Proteome-Based Pathway Modelling of Psychiatric Disorders. Publication with The max Planck Institute of Psychiatry in Munich
- 2010, INFECTIOUS DISEASES: Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science :Genetically Engineered Virulent Phage Banks in the Detection and Control of Emergent Pathogenic Bacteria. Publication with Pherecydes-Pharma.
- 2009, TISSUE DIFFERENTIATION: Médecine & Sciences: Müllerian duct regression explanation. Integrative systems biology & experimental Biology. Publication with CNRS experimental data.
- 2005, CANCER: Journal of molecular Endocrinology: Integrative analysis of gene expression patterns predicts specific modulations of defined cell functions by estrogen and Tamoxifen in MCF7 breast cancer cells. Publication in collaboration with INSERM unit 553.
- 2003, CANCER: Nucleic Acids Research: Integrated transcriptome analysis of the cellular mechanisms associated with H-ras-dependent malignant transformation of the human breast epithelial MCF7 cell line. Publication in collaboration with INSERM unit 553. World first. First in-silico model of a complex human disease validated in-vitro and published.

**Collaboration to scientific reference books:**

- 2014: Dermatology Cosmetics. The first reference book on "Computational Biophysics of the Skin" edited by Prof. Bernard Querleux , scientific chairperson of the International Society for Biophysics and Imaging of the Skin
- 2011: Phage Nano Technology book published by Valery Petrenko. Chapter 8: Genetically Engineered Virulent Phage Banks for the Detection and Control of Bacterial Biosecurity Threats.
- 2008: CNS: Biomarkers for Psychiatric Disorders. (Ref. ISBN: 978-0-387-79250-7, November 2008). Dr. François Iris, is the author of the Integrative Biology chapter of the book. The editor, Prof. Christoph W. Turck, is head of the Proteomics and Biomarkers branch at the Max Planck Institute for Psychiatry

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# BMSystems' 10 CADI™ programs & POCs

## Selected POCs and their outputs of CADI™ Programs (next slides):

1. Case study A; Domain: CNS neurology and Psychiatry. Collaborative CADI™ program with CEA life sciences (*1 patent, 1 publication, 1 spin-off*).
2. Case study B; Domain: Metabolism: First disease application: Parkinson's disease. Collaborative CADI™ program (*novel combined therapy proposed for POC in humans*).
3. Case study C; Domain: Infectious diseases. Collaborative CADI™ program with Pherecydes-Pharma (our first spin-off) (*3 patents, 1 publication, 1 spin-off*).
4. Case study D; Domain: Industrial biotech. Collaborative CADI™ program with ARD, IBT, CVG, L'Oréal, Rhodia, Arkema (*1 patent filed by an industrial partner*).
5. Case study E: Domain: Synthetic biology: Yeast-Based Human-Glycoylation Project CADI v0 produced
6. Case study F; Domain: Oncology. Collaborative CADI™ program with Inserm unit 553 (*2 publications, Novel strategy proposed for R&D collaboration*)
7. Case study G; Domain: Dermatology. Contractual program CADI™ for a client (*8 new targets, cosmetic company confidential*).
8. Case study H; Domain: Cosmetics. Collaborative CADI™ program) *(synergistic low allergy mechanisms identified for safety issues).*
9. Case study I; Domain: Type 2 diabetes. Contractual CADI™ program for a client (*NO GO decision for safety issue, pharma company, confidential*).
10. Case study J; Domain: Tissue differentiation/embryogenesis. Collaborative CADI™ program with CNRS (*1 publication*).

**A new paradigm qualified for industrial use**



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# Useful Downloads

**Download the Full Presentation with CADI Description, publications and the 10 CADI programs & POCS**

## For more information about information quality & reliability

- A new evidence published in Sciences confirms the poor reproducibility (less than 1/3) of studies published in peer-reviewed.
- An estimated 85% of current published research findings are false or exaggerated: How to Make More Published Research True. Published in PLOS Medicine by John P. A. Ioannidis Meta-Research Innovation Center at Stanford (METRICS), Stanford University.
- Diagnosing the decline in pharmaceutical R&D efficiency. Published Nature Review Drug Discovery. The diagnostic is clear for our industry.
- Believe it or not: how much can we rely on published data on potential drugs targets? Their title is crystal clear. Published Nature Review Drug Discovery

## Heuristic modeling principles and case studies

- **Request our Cochin Institute Paris "Integrative Analyses" Training Session Presentation**
- The discovery of Innovative Therapeutic Approaches: Under the street light is not the right place to search BIT's 10th Annual Congress International Drug Discovery Science and Technology 2012 November 8-10, 2012, Nanjing, China
- The Differences & Complementarities Between « Heuristic » and « Mathematical» approaches. The scientific presentation given by Dr. François IRIS (CSO BMSystems) during the EPA (European Psychiatric Association) conference in 2011.

## Author's LinkedIn Posts: https://www.linkedin.com/today/author/871235

- The future will be digital & biology, but who will lead?
- Therapeutic innovation is moving faster than it may appear and this may be of interest to you.
- Alzheimer drugs failures. Why not a good news for patients!
- Big Data = Big garbage? An estimated 85% of research resources are wasted! 6 documents to read.
- Who is the number 1 serial killer of disruptive innovations in biomedical research?

Email: manuel.gea@bmsystems.net Join my networks

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