ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
European Society for Medical Oncology

European School of Oncology
Learning to care

RARE CANCERS EUROPE
Joining forces for action

Training Course for Rare Cancer Patient Advocates
2-4 December 2017 in Milan (Pilot Course)

Targeted therapies and precision oncology

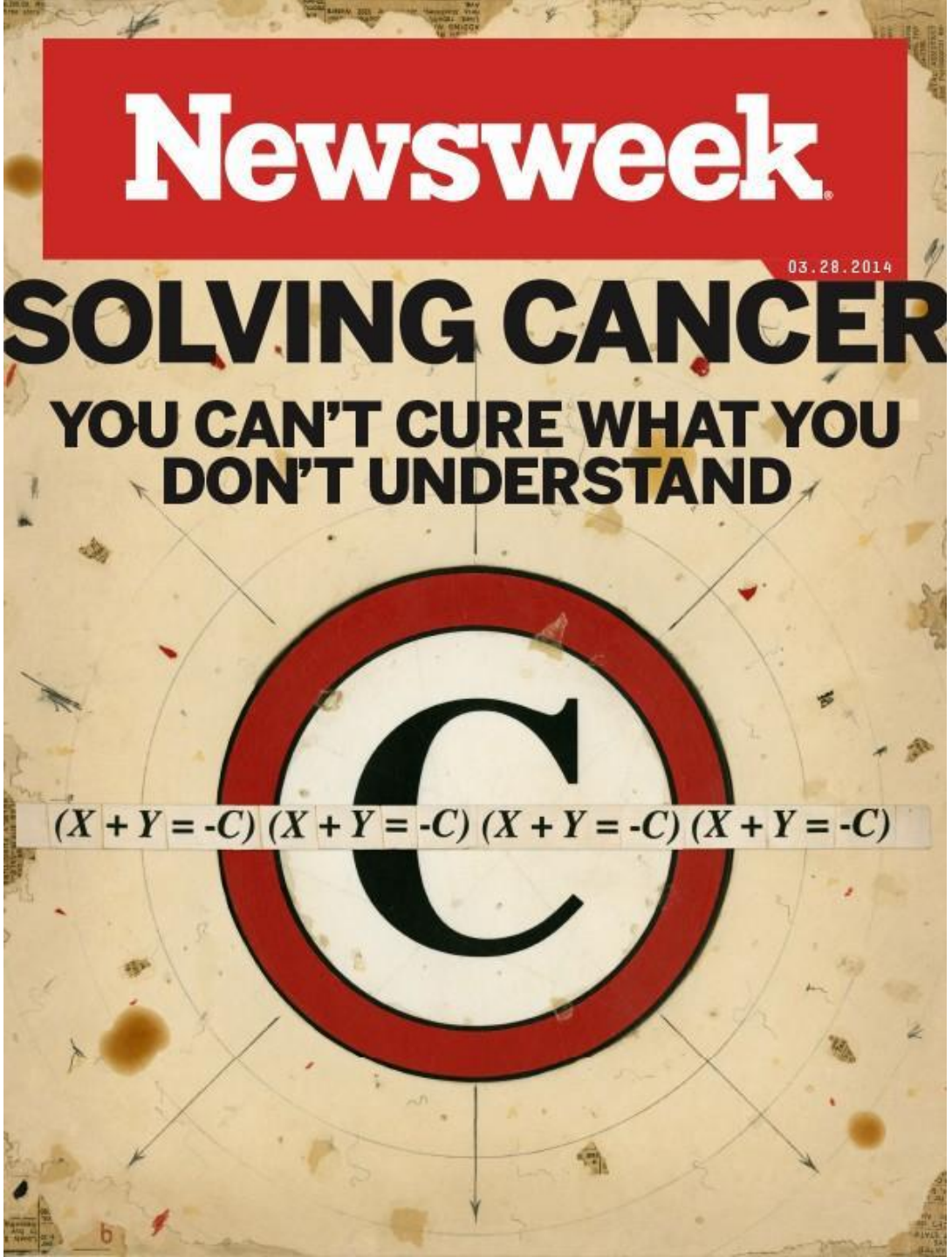
Nicola Fazio, M.D., Ph. D.

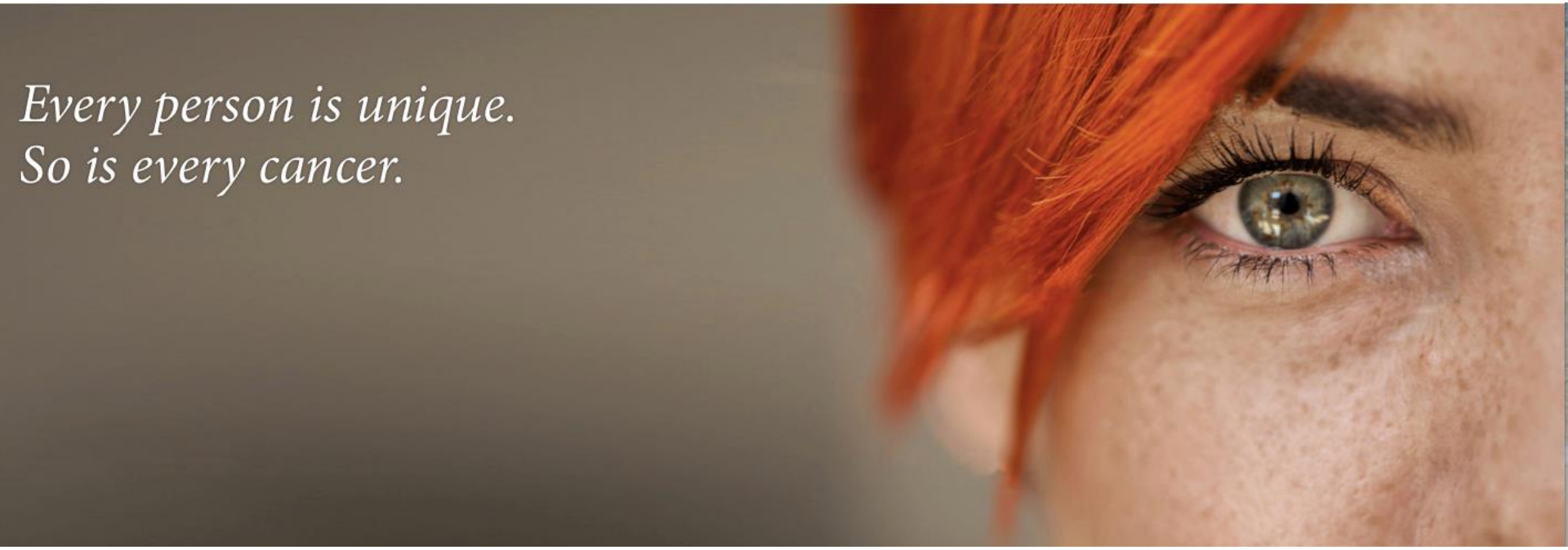
Division of Gastrointestinal Medical Oncology
and Neuroendocrine Tumors
European Institute of Oncology
Milan, Italy

Newsweek
03.28.2014

SOLVING CANCER

YOU CAN'T CURE WHAT YOU DON'T UNDERSTAND




Every person is unique.
So is every cancer.

NIH NATIONAL CANCER INSTITUTE

Targeted Cancer Therapies

What are targeted cancer therapies?

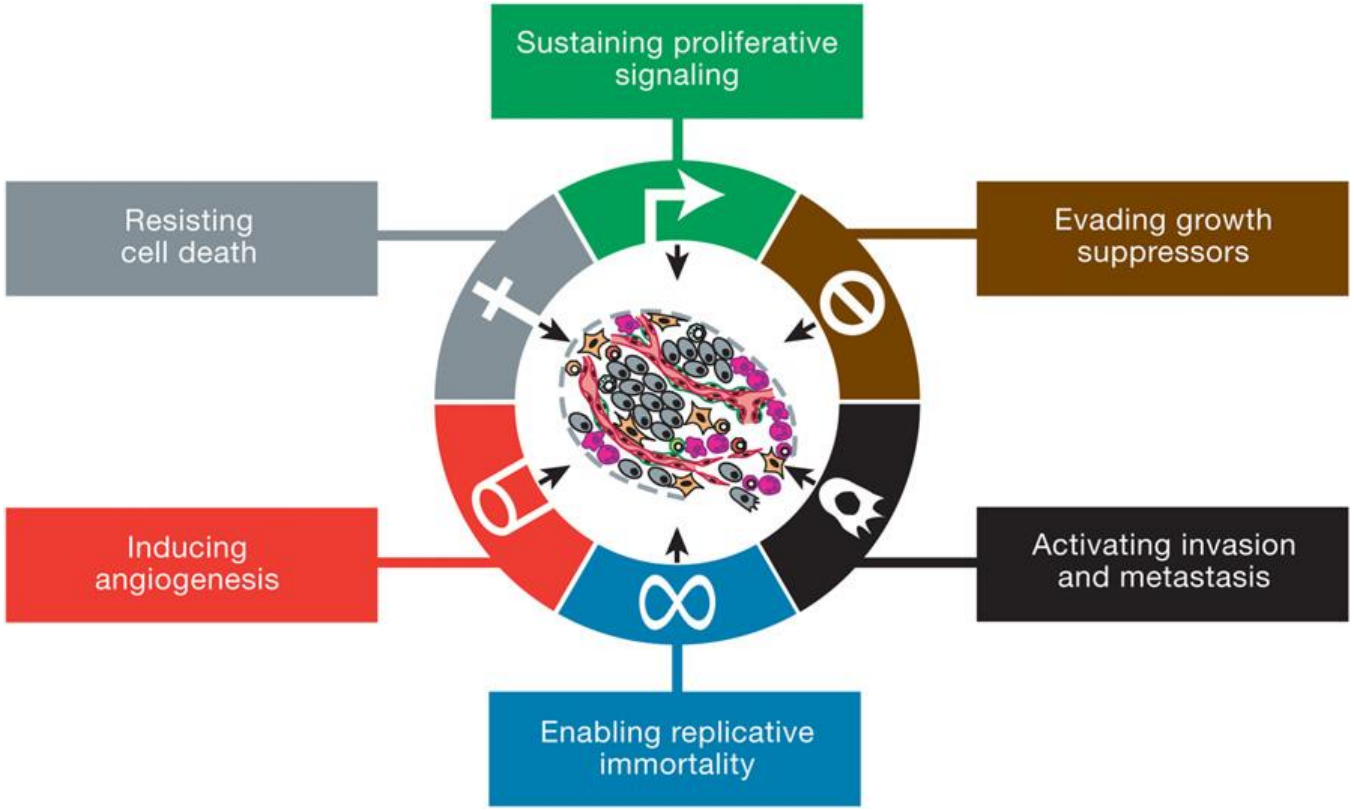
Targeted cancer therapies are drugs or other substances that block the growth and spread of cancer by interfering with specific molecules ("molecular targets") that are involved in the growth, progression, and spread of cancer. Targeted cancer therapies are sometimes called "molecularly targeted drugs," "molecularly targeted therapies," "precision medicines," or similar names.

Hallmarks of Cancer: The Next Generation

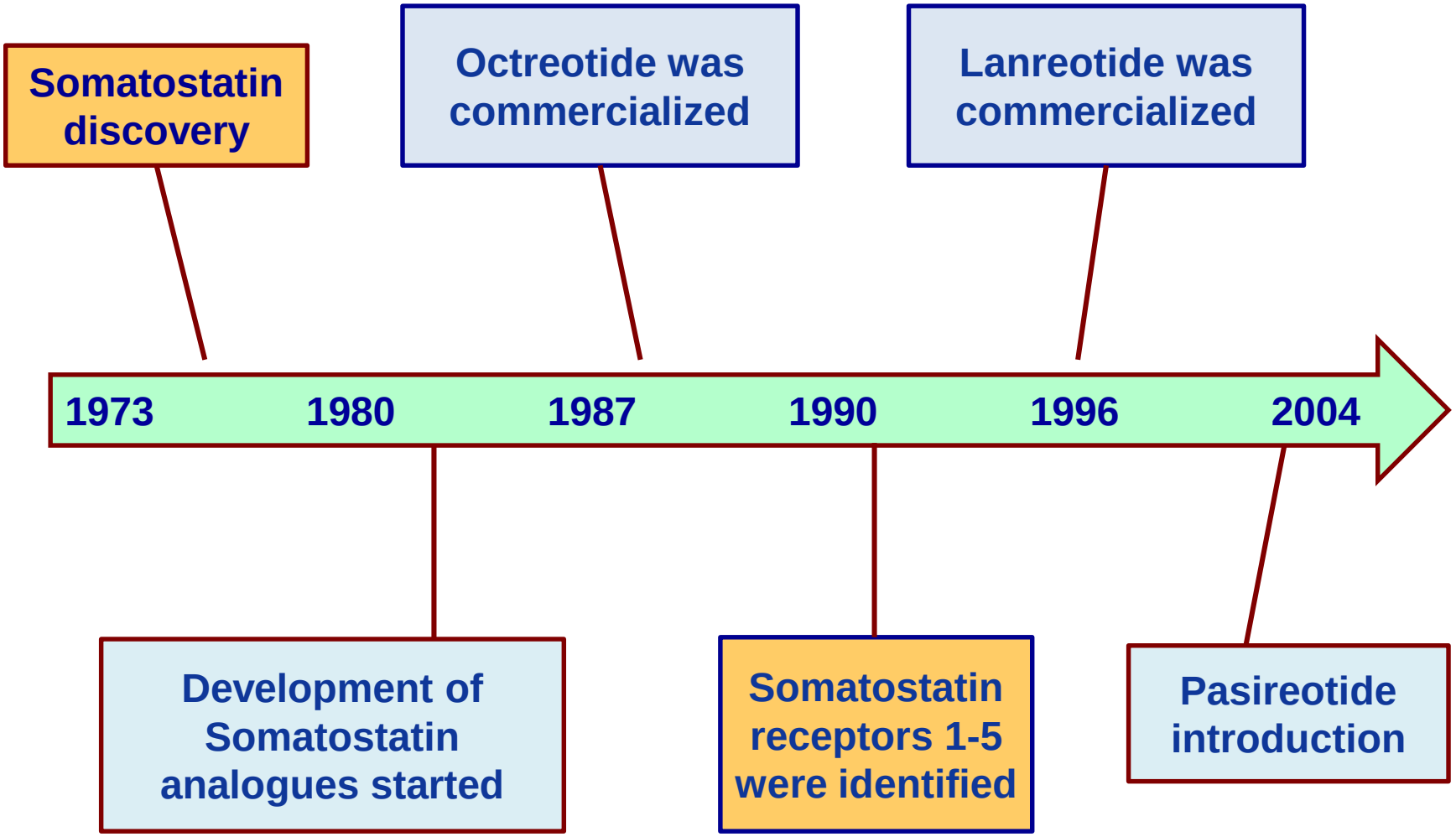
Douglas Hanahan[1,2,*] and Robert A. Weinberg[3,*]

Cell *144*, March 4, 2011 ©2011 Elsevier Inc.

Six Cell-autonomous mechanisms to control early oncogenesis



Somatostatin analogues: history



Targeted therapy is different from conventional chemotherapy

Targeted therapies differ from standard chemotherapy in several ways:

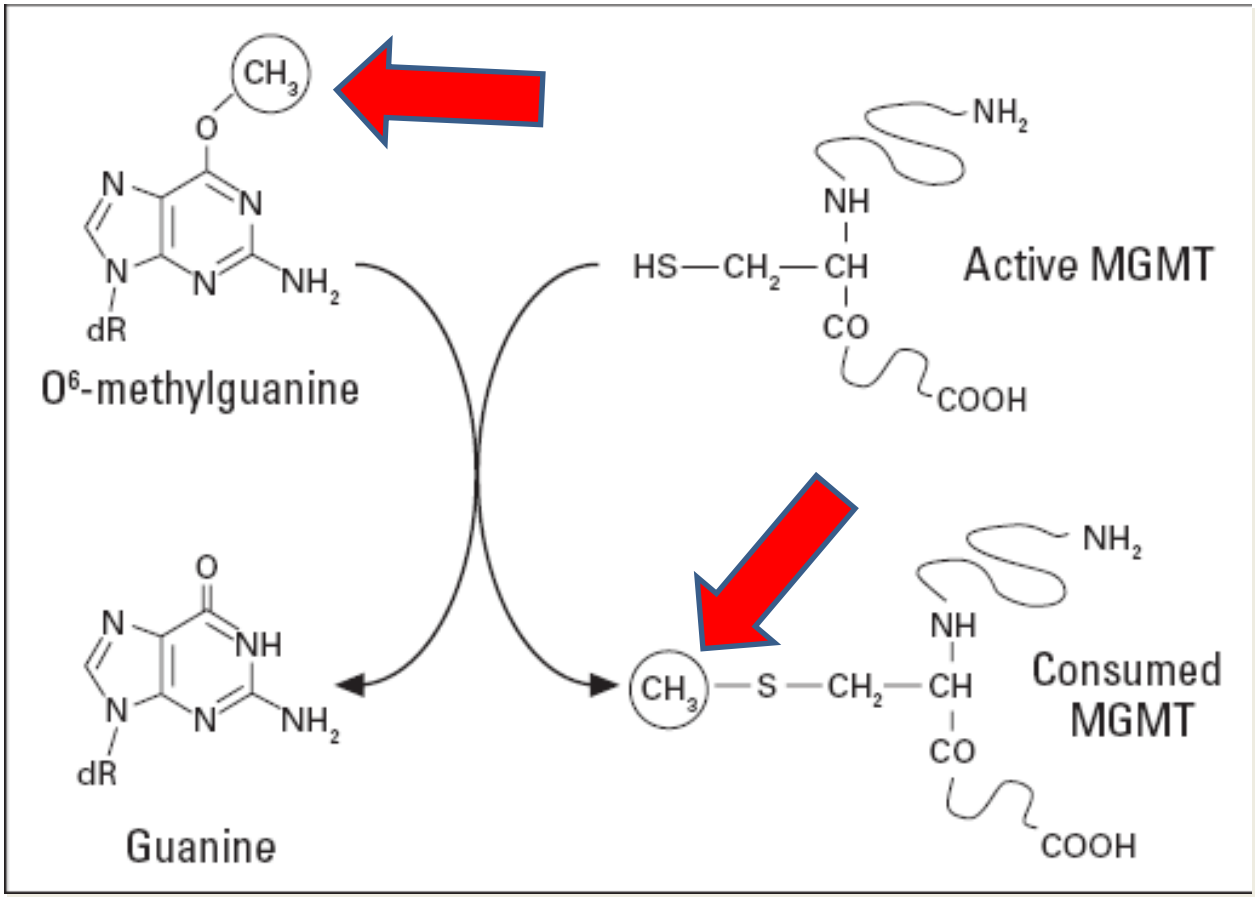
- Targeted therapies act on specific molecular targets that are associated with cancer, whereas most standard chemotherapies act on all rapidly dividing normal and cancerous cells.
- Targeted therapies are deliberately chosen or designed to interact with their target, whereas many standard chemotherapies were identified because they kill cells.
- Targeted therapies are often cytostatic (that is, they block tumor cell proliferation), whereas standard chemotherapy agents are cytotoxic (that is, they kill tumor cells).

Chemotherapy can be a targeted therapy

Streptozocin (STZ)

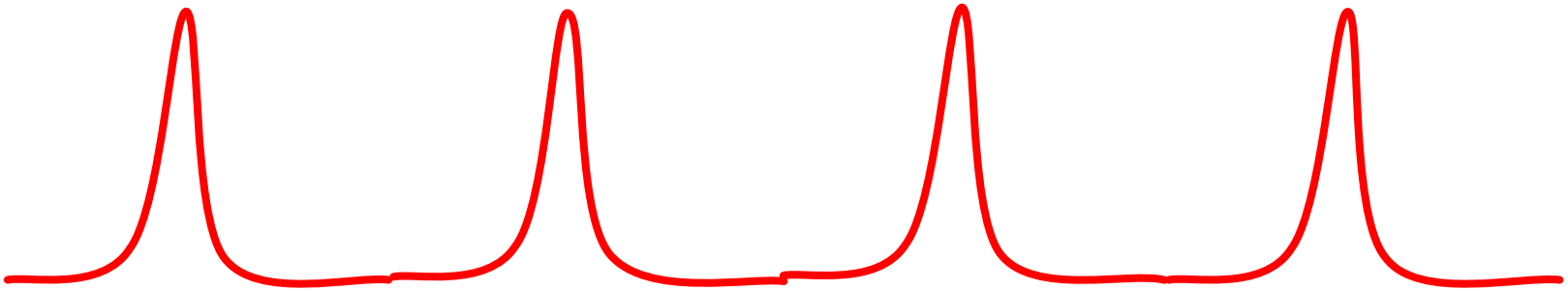
Dacarbazin (DTIC)

Temozolomide (TMZ)


CH3
O
N
N
N
N
NH2
dR
O6-methylguanine
NH2
NH
HS—CH2—CH
CO
COOH
Active MGMT
O
N
NH
N
N
NH2
dR
Guanine
CH3—S—CH2—CH
NH2
NH
CO
COOH
Consumed MGMT

Metronomic chemotherapy is a personalised therapy

“CONVENTIONAL”



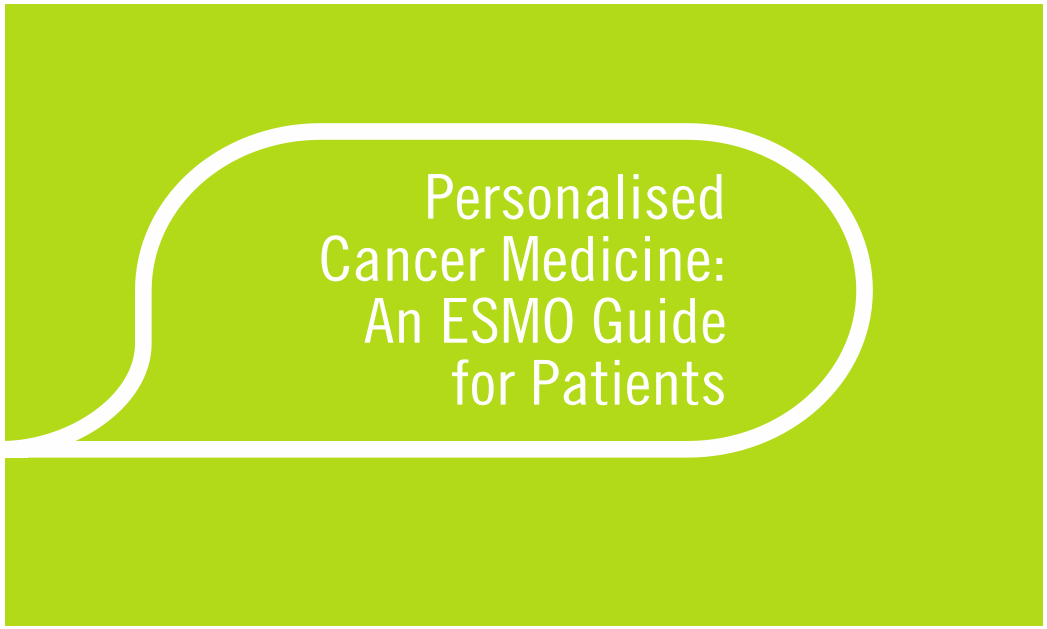
Maximum Tolerated Dose (MTD)

“METRONOMIC”

Continuative low dose

Browder et al., Cancer Res 2000

Personalised cancer management – which means giving patients the optimum treatment according to their individual circumstances (including their genetics) and the molecular characteristics of their tumours – was a key theme of ESMO in 2013.



Preface Comment

Martine Piccart

ESMO President

Fortunato Ciardiello

Chair of the ESMO Personalised Medicine Task Force

ESMO Supported 2013 World Cancer Day by Cautioning That the Era of Personalised Cancer Medicine Is Not Here Yet

"Personalised medicine is the dream of every oncologist and the legitimate expectation of every cancer patient," says Professor Martine Piccart, ESMO President. "However, currently we are not yet in the era of personalised oncology but in the era of stratified oncology, which means we are able to classify cancers according to critical targets against which we hope to develop effective drugs. Modern technologies such as deep DNA sequencing will be powerful tools in the future allowing us to identify drugable mutations*."

Personalised Medicine: General Definition

Personalised management is considered as the future of cancer care: medicine aiming at giving patients the best treatment according to their personal medical history, their physiological status, and the molecular characteristics of their tumours.

The longer-term promise of personalised medicine is not only to more effectively treat patients, but also to prevent disease based not only upon genetic prediction but also upon physiological status over the patient's lifetime.

In 2012 there were 2.6 million people in the European Union (EU) with newly diagnosed cancer.

Although early detection and improved treatments are saving many lives, cancer is still the second most frequent cause of mortality and is responsible in the EU for an annual 1.3 million deaths. With an ageing population, the cancer burden in the EU is projected to continue rising to 3.2 million new diagnoses and 1.7 million cancer deaths in 2030.


PRECISION℠
ONCOLOGY
PART OF PRECISION FOR MEDICINE

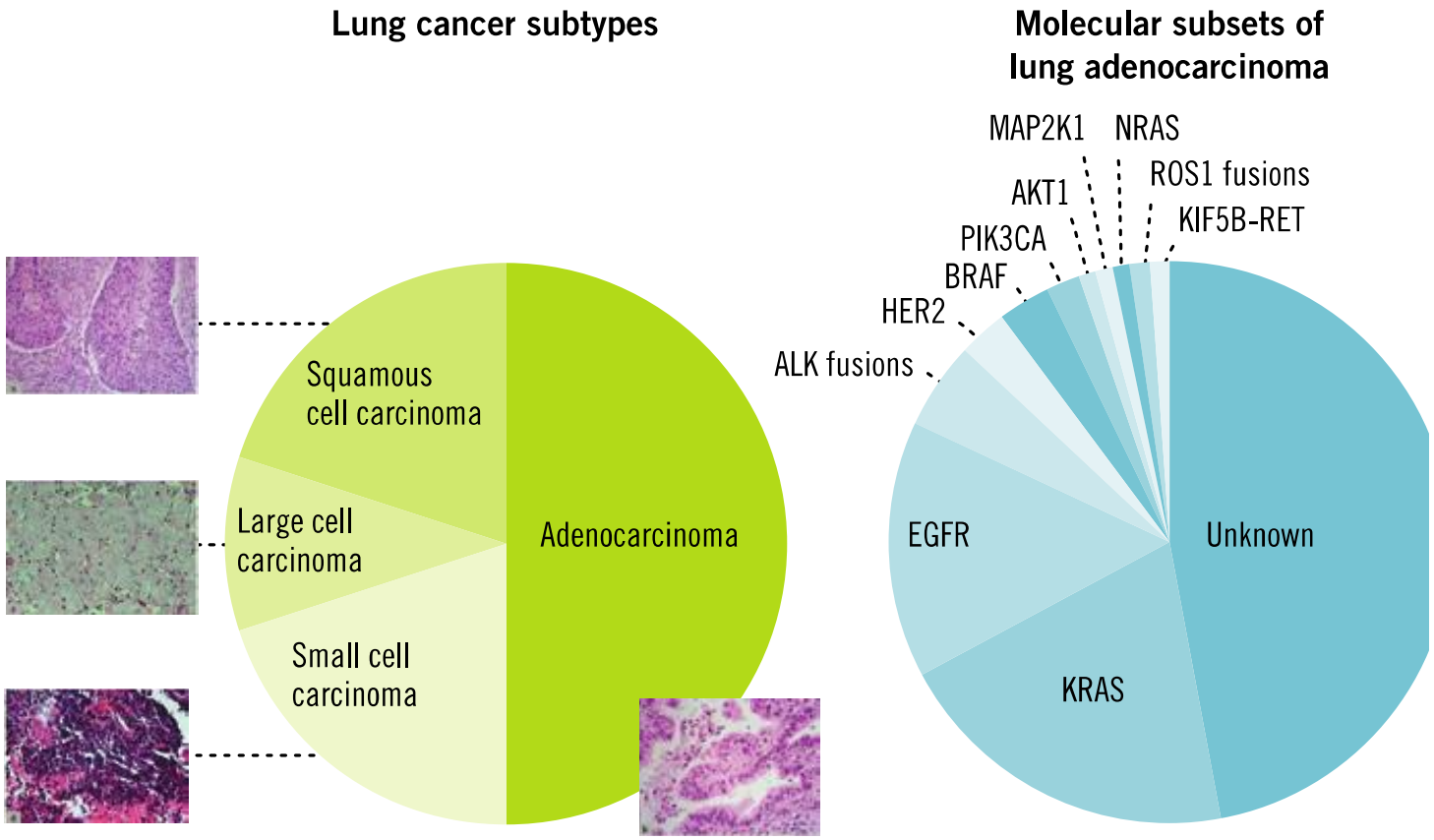
Fortunato Ciardiello
Chair of the ESMO Personalised Medicine Task Force

Personalised medicine comes from the results of research efforts over the past 20 to 30 years to understand the complexity of cancer. Not only between different tumour types and organs, but also within any tumour, there is enormous heterogeneity.

As a result, an approach of providing the same kind of therapy to the same patients just because their tumours arise in the same organ – breast, lung, prostate or whatever – will be effective in general, but does not work for everyone, unfortunately.

Figure 2. Lung Cancer – Not One Disease: Histological (Tissue) and Molecular Subtypes of Lung Cancer.

On the left side, four histological subtypes of lung cancer. On the right side, a pie chart showing th percentage distribution of molecular subsets of lung adenocarcinoma.



Adapted from Petersen I. Dtsch Arztebl Int 2011; 108(31-32):525-531 (left) and Pao W & Hutchinson KE. Nature Med 2012; 18(3): 349-351, with permission.

Angelo Paolo Dei Tos

Pathologist, ESMO Faculty

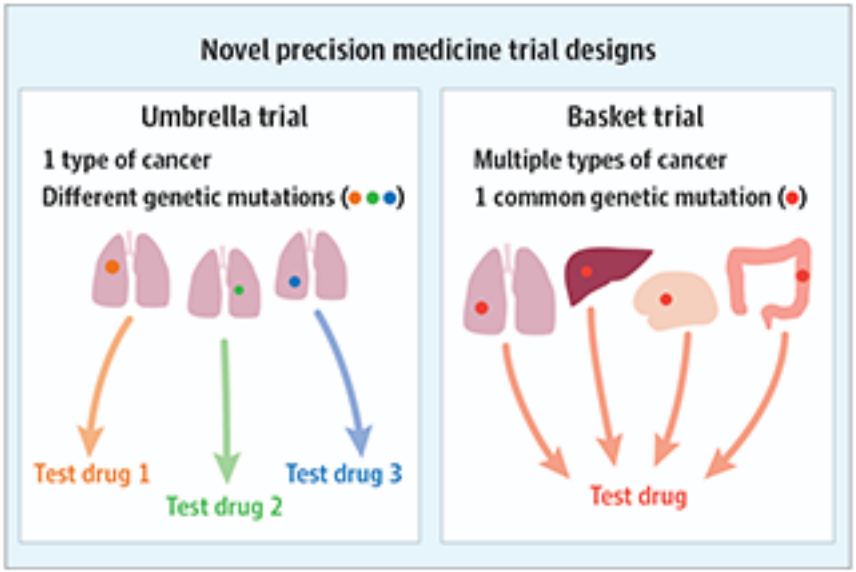
"You need to give a name to a tumour, and a pathologist is the professional who gives a name to tumours. The variety of cancers is broad; when we say "sarcoma", "carcinoma", or "lymphoma", we actually say nothing, ……."

That's particularly true also for NET, where sometimes false hopes have been fed

" Neuroendocrine "

Clinical trials for precision oncology

Basket Trial: Basket trials (or studies) test the effect of one drug on a single mutation in a variety of tumor types, at the same time. These studies also have the potential to greatly increase the number of patients who are eligible to receive certain drugs relative to other trials designs.



JAMA Oncology: doi:10.1001/jamaoncol.2016.5299

Umbrella Trial: Umbrella trials (or studies) have many different treatment arms within one trial. People are assigned to a particular treatment arm of the trial based on their type of cancer and the specific molecular makeup of their cancer.

Personalised medicine can be described as:

"The right medicine for the right patient at the right time".

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

FEBRUARY 26, 2015

A New Initiative on Precision Medicine

Francis S. Collins, M.D., Ph.D., and Harold Varmus, M.D.

> "Tonight, I'm launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes — and to give all of us access to the personalized information we need to keep ourselves and our families healthier."
>
> — President Barack Obama, State of the Union Address, January 20, 2015

is a broad research program to encourage creative approaches to precision medicine, test them rigorously, and ultimately use them to build the evidence base needed to guide clinical practice.

The proposed initiative has two main components: a near-term

“In February 2015, President Obama brought together experts in medicine, science, and technology to announce the creation of the Precision Medicine Initiative (PMI), with the bold goal to accelerate biomedical discovery and give clinicians new tools, knowledge, and therapies to tailor treatments to individuals.”

By DJ Patil, Chief Data Scientist in the White House Office of Science and Technology Policy, and Stephanie Devaney, Project Manager of the Precision Medicine Initiative

President Obama has specifically requested a $215 million investment,

"Tonight I'm launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes.

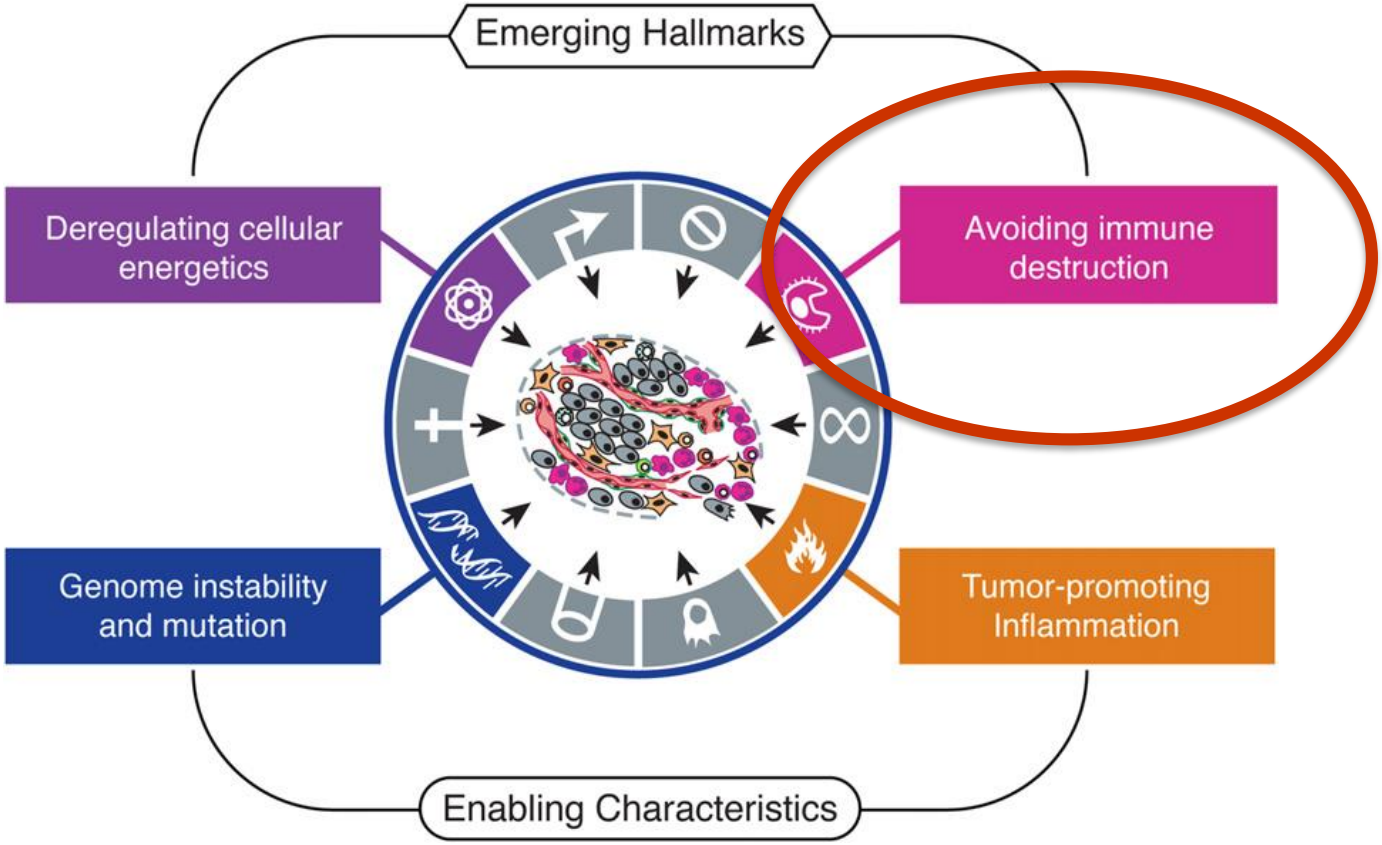
And to give us all access to the personalized information we need to keep ourselves and our families healthier."

President Barack Obama
2015 State of the Union Address | January 20, 2015

Most importantly he included patients like Elana Simon—a college student, cancer survivor and cancer researcher—to emphasize that in every aspect of PMI, individuals of all backgrounds will be partners and collaborators.

Two additional hallmarks of cancer

The second allows cancer cells to evade immunological destruction, in particular by T and B lymphocytes, macrophages, and natural killer cells.



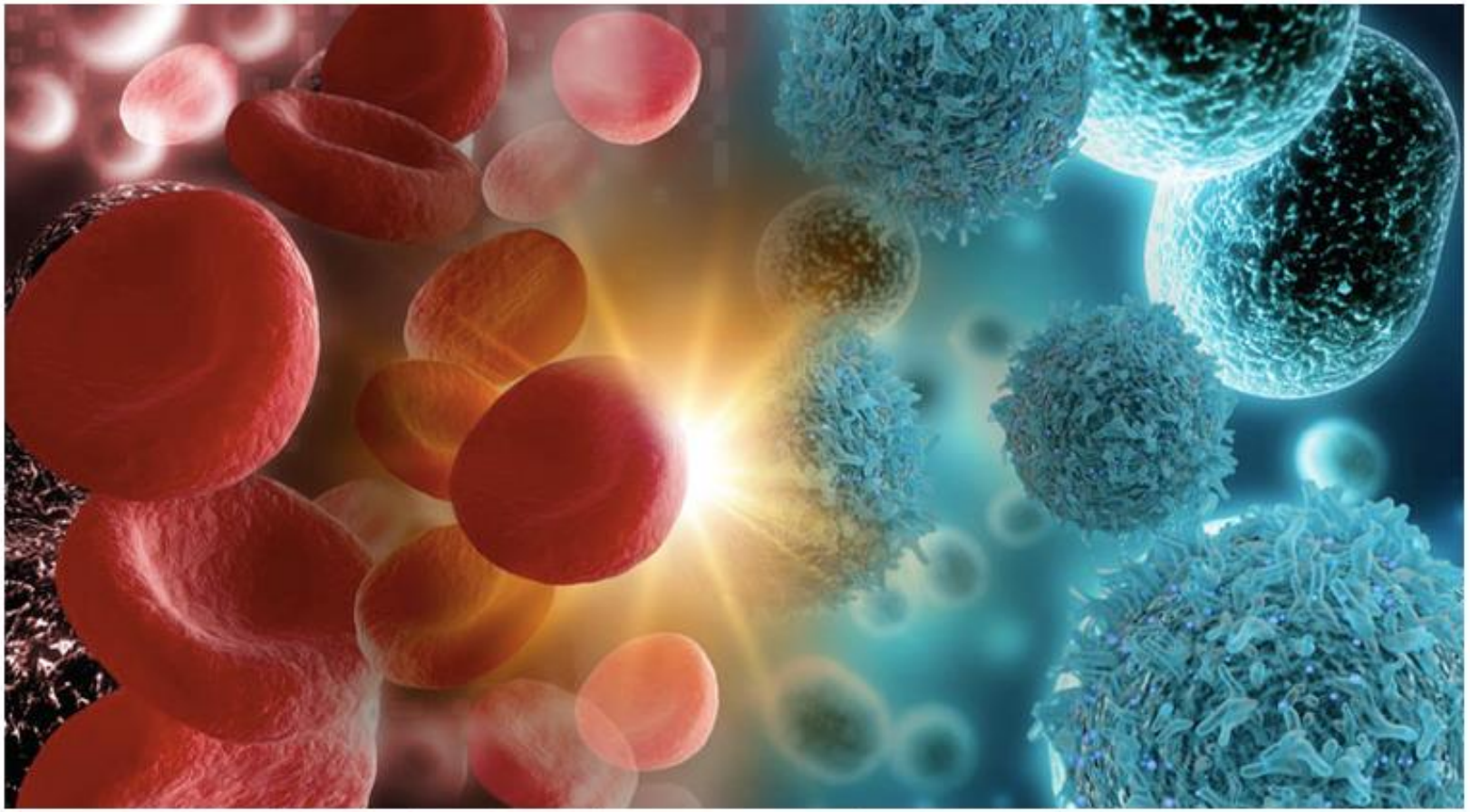
Hanahan, Cell 2011

The Immunotherapy Revolution

Miriam A. Knoll, MD

Immunotherapy is changing the face of oncology, giving patients a new way to fight cancer and to live longer. How it works and what you need to know

Wednesday, June 21, 2017



THE BODY STRIKES BACK Chemotherapy refers to drugs that kill cancer cells or stop them from dividing. This differs from immunotherapy, which are drugs that enable the body's immune system to better kill cancer cells

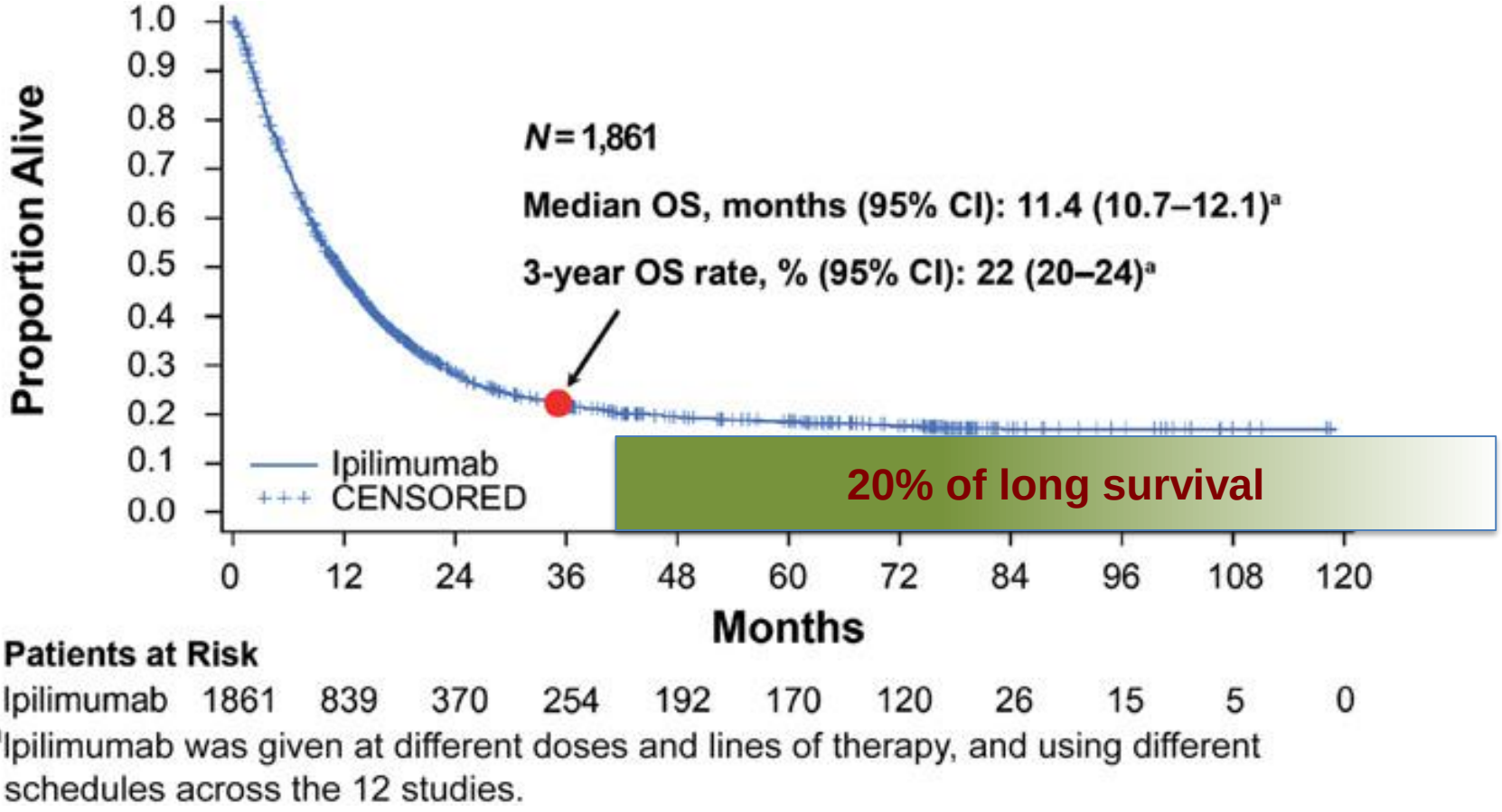


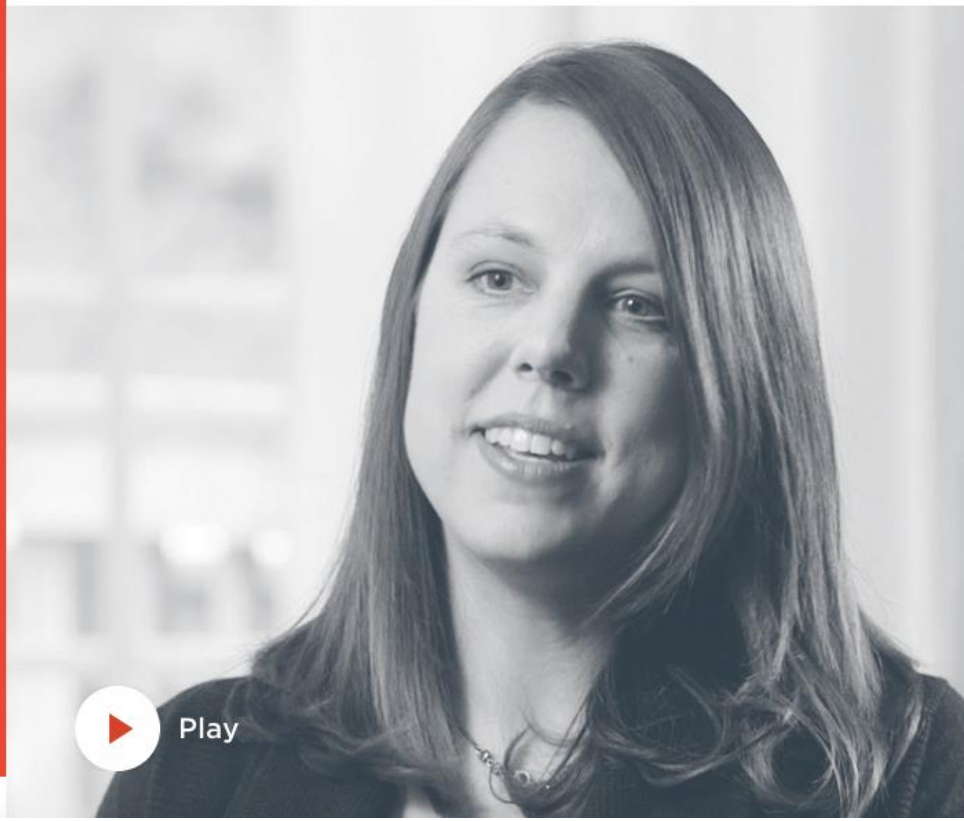
Figure 5. Long-term survival in melanoma patients treated with ipilimumab: results of a pooled analysis. From [74] with per-

Pennock et al., Oncologist 2015

PATIENT STORY

"Dealing with cancer is not just dealing with the cancer. It's treating the whole person."

Christine Bray, ovarian cancer survivor, shares her journey to remission after obtaining FoundationOne®, a comprehensive genomic profiling test.



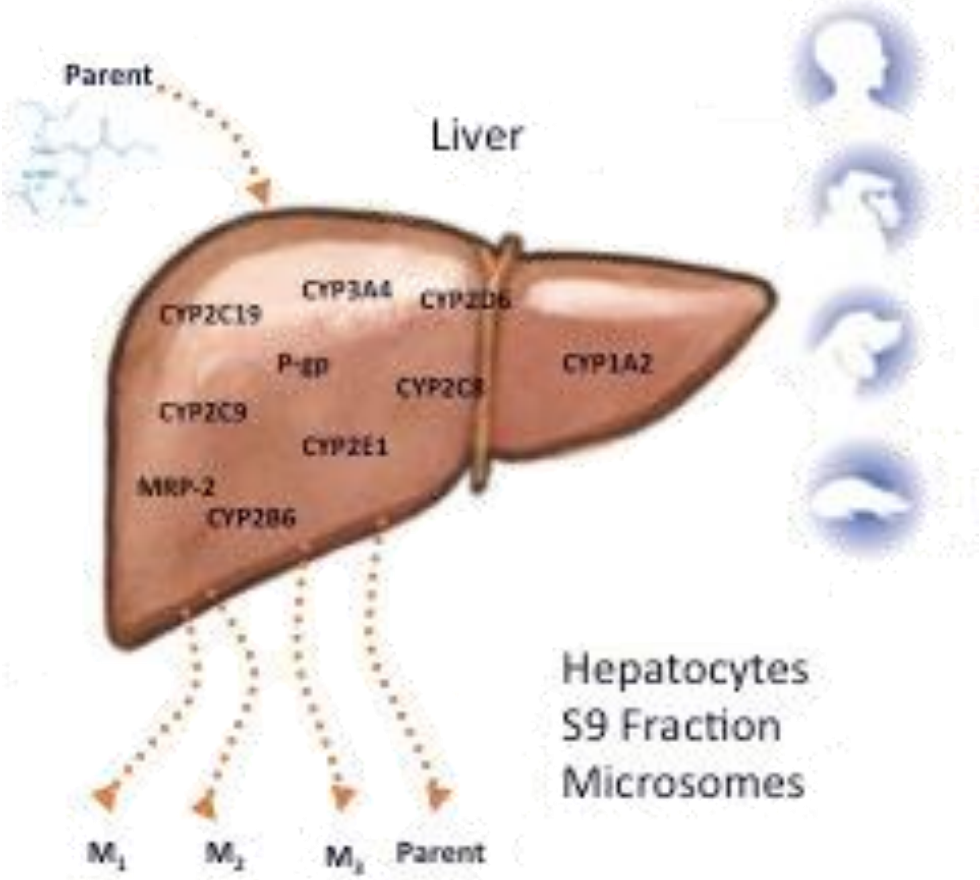
First of all, personalisation requires ***the humanisation of medicine****.*

"We know that these technologies have led to less effective face-to-face interaction between patient and doctor. It will be very hard, for example, to start talking to patients about the evaluation of 255 genes that may be altered in a tumour that metastasises to the brain; ***we need to begin seeing through the eyes of our patients. "***

*So personalisation starts with **an individual relationship** on the part of the physician and the medical team who are taking care of the patient.*

The right medication in the wrong patient

Genetic alterations of the liver metabolism of drugs



mTOR inhibitors

	Sirolimus	Everolimus	Temsirolimus	Ridaforolimus (Deforolimus)
Brand name	**Rapamune®**	**Certican® Afinitor®**	**Torisel®**	**Taltorvic®**
Formulation	**oral**	**oral**	**I.V.**	**I.V.**
Indication	**Prevent renal rejection**	**Prevent renal/heart rejection, NET, RCC, Breast cancer, SEGA, renal angiomyolipomas associated with TS**	**RCC, MLC**	**Soft tissue sarcoma**

NET= neuroendocrine tumor; RCC = renal cell carcinoma; SEGA = subependymal giant cell astrocytoma; TS = tuberous sclerosis; I.V. = intravenous

From the Easter island ……

In 1964 a Canadian researchers expedition from the Ayerst-Wyeth Pharmaceuticals traveled to Easter island to gather soil samples and plants.

In 1972 the expedition team and a microbiology team identified and isolated RAPAMYCIN from the mycobacterium Streptomyces Hygroscopicus

Sehgal et al., J Antibiot (Tokyo) 1975
Vezina et al., J Antibiot (Tokyo) 1975

Rapamycin properties

Several years later Rapamycin demonstrated antifungal activity blocking the G1 to S phase of the cell cycle.

The block of G1 to S phase of the cell cycle in T-lymphocytes revealed a potent immunosuppressant activity of Rapamycin in mammalians.

Sehgal et al., J Antibiot (Tokyo) 1975
Vezina et al., J Antibiot (Tokyo) 1975
Heitman et al., Science 1991
Thomson et al., Nat Rev Immunol 2009

The birth of the Rapalogs

Rapamycin demonstrated antiproliferative activity in vitro and in vivo in human tumor xenografts implanted into immunosuppressed mice

Rapamycin and its analogs (globally called **RAPALOGS**) were developed in organ transplantation and oncology, starting from the Biozentrum (Basel) and Sandoz Pharmaceuticals (now Novartis) laboratories.

Heitman et al., Science 1991

The molecular target of rapamycin

Two classes of resistant yeast had mutations in genes named TOR1 and TOR2 in honor of the Spalentor, a gate of the city of Basel, where TOR was first discovered.

Heitman et al., Science 1991

mTOR = master switch

Oxidative stress

GROWTH FACTORS
(IGF, EGF, PDGF, VEGF)

NUTRIENTS
(glucose, cholesterol, iron, zinc)

Insulin

mTOR

Aminoacids

CELL GROWTH

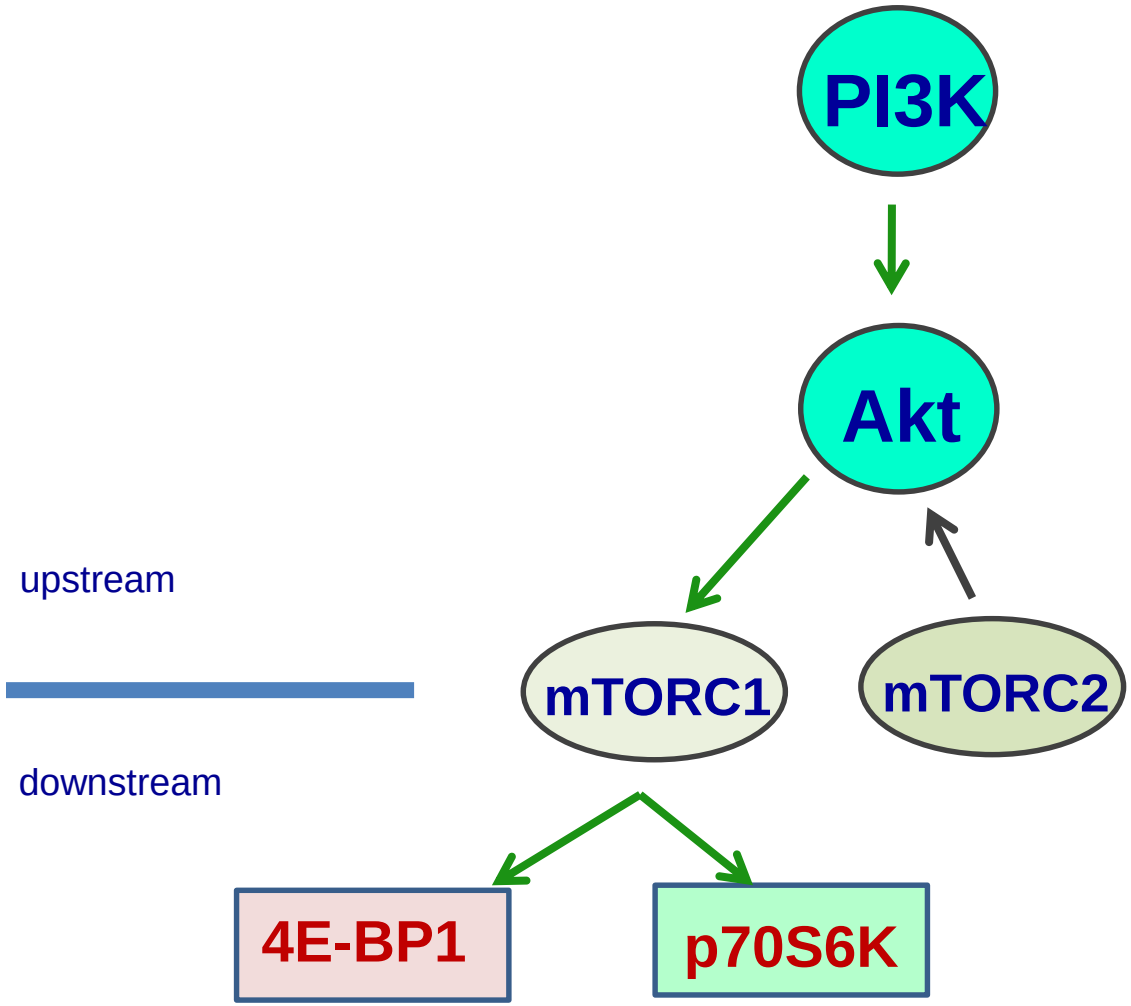
PROLIFERATION

ANGIOGENESIS

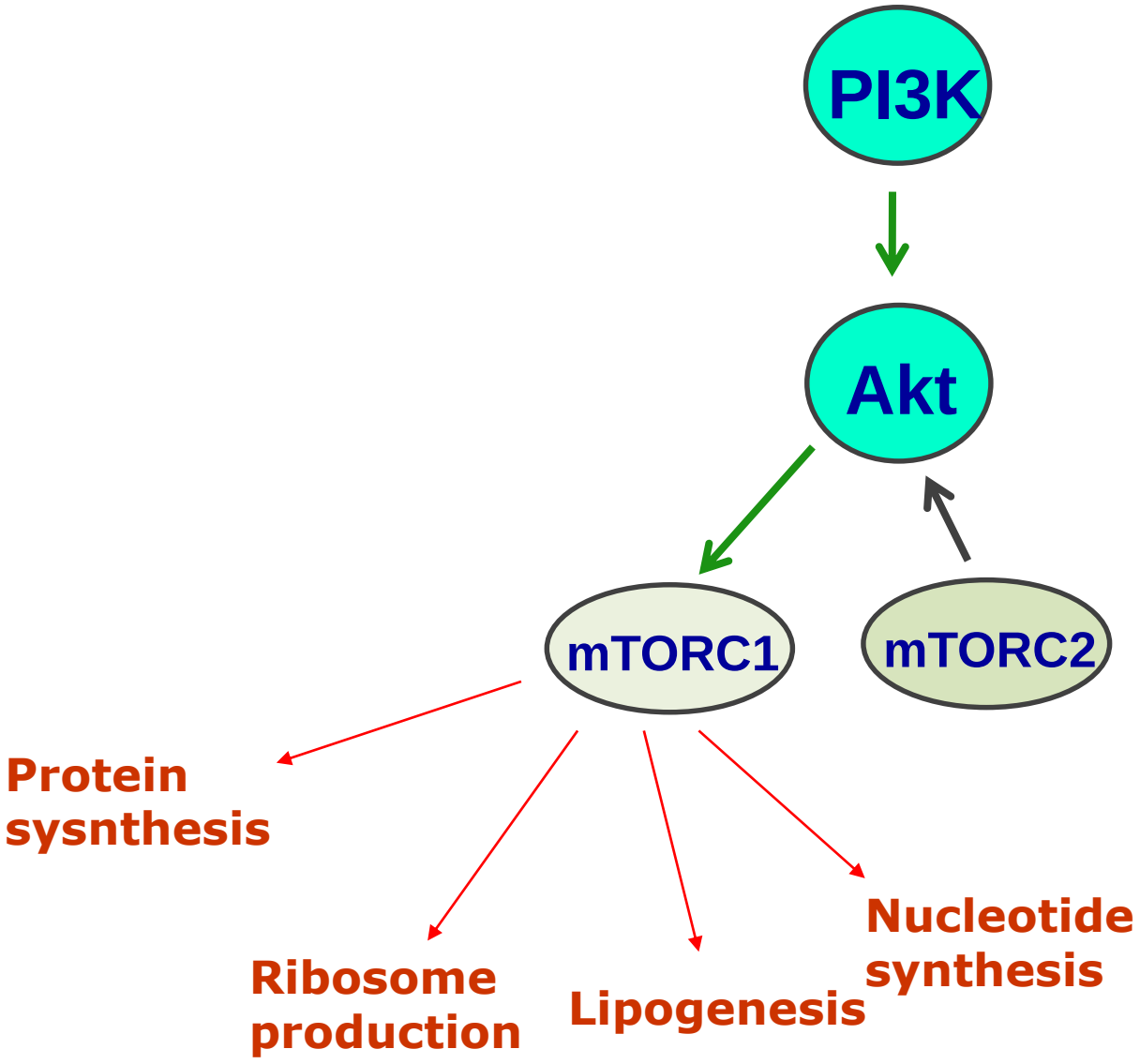
BIOENERGETICS

Barbet et al., Mol Biol Cell 1996

The pathway of mTOR

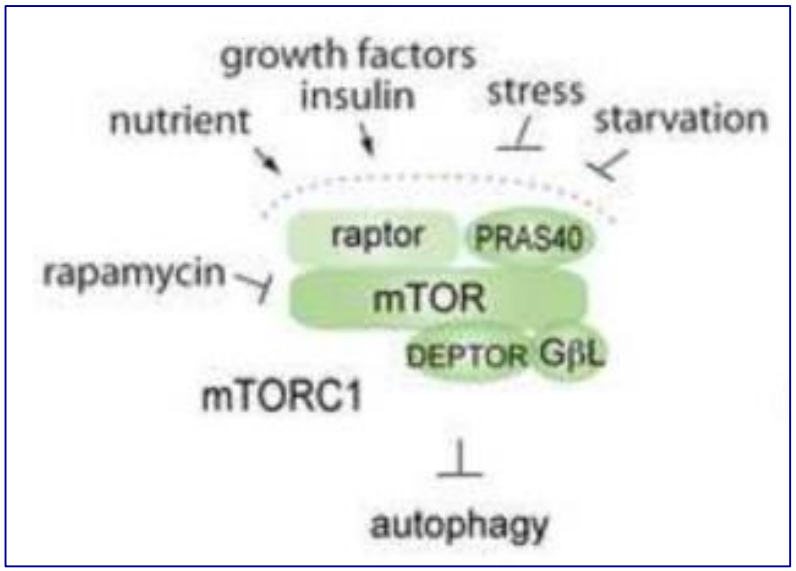


Functions of mTORC1



mTORC1 physiologically suppresses autophagy.

NUTRIENT STARVATION



mTOR

mTORC1 inhibition either pharmacologically or by "nutrient deprivation" leads to induction of autophagy

AUTOPHAGY

Jung et al., FEBS Lett 2010

2016 NOBEL PRIZE FOR PHYSIOLOGY OR MEDICINE TO YOSHINORI OHSUMI FOR AUTOPHAGY

Nobelförsamlingen
The Nobel Assembly at Karolinska Institutet

The Nobel Assembly at Karolinska Institutet has today decided to award

the 2016 Nobel Prize in Physiology or Medicine

to

Yoshinori Ohsumi

for his discoveries of mechanisms for autophagy

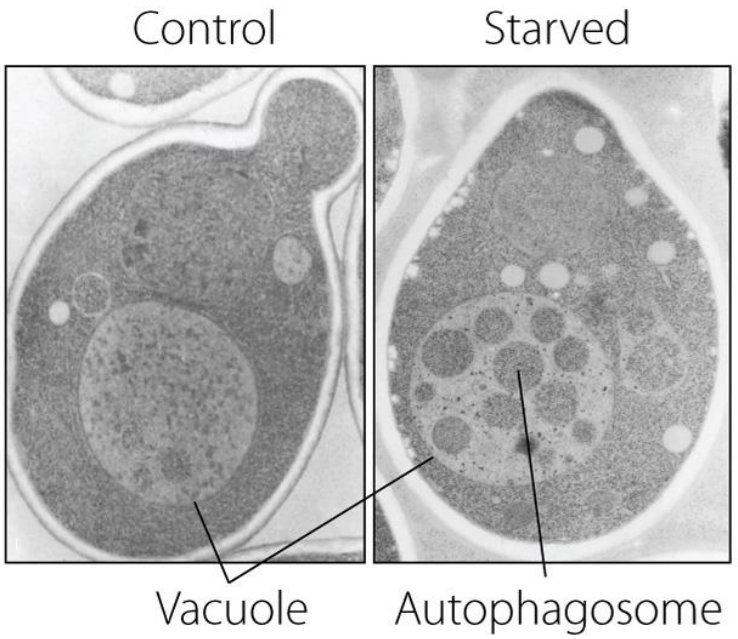
Autophagy = self eating

The cell can destroy its own components forming the lysosomes

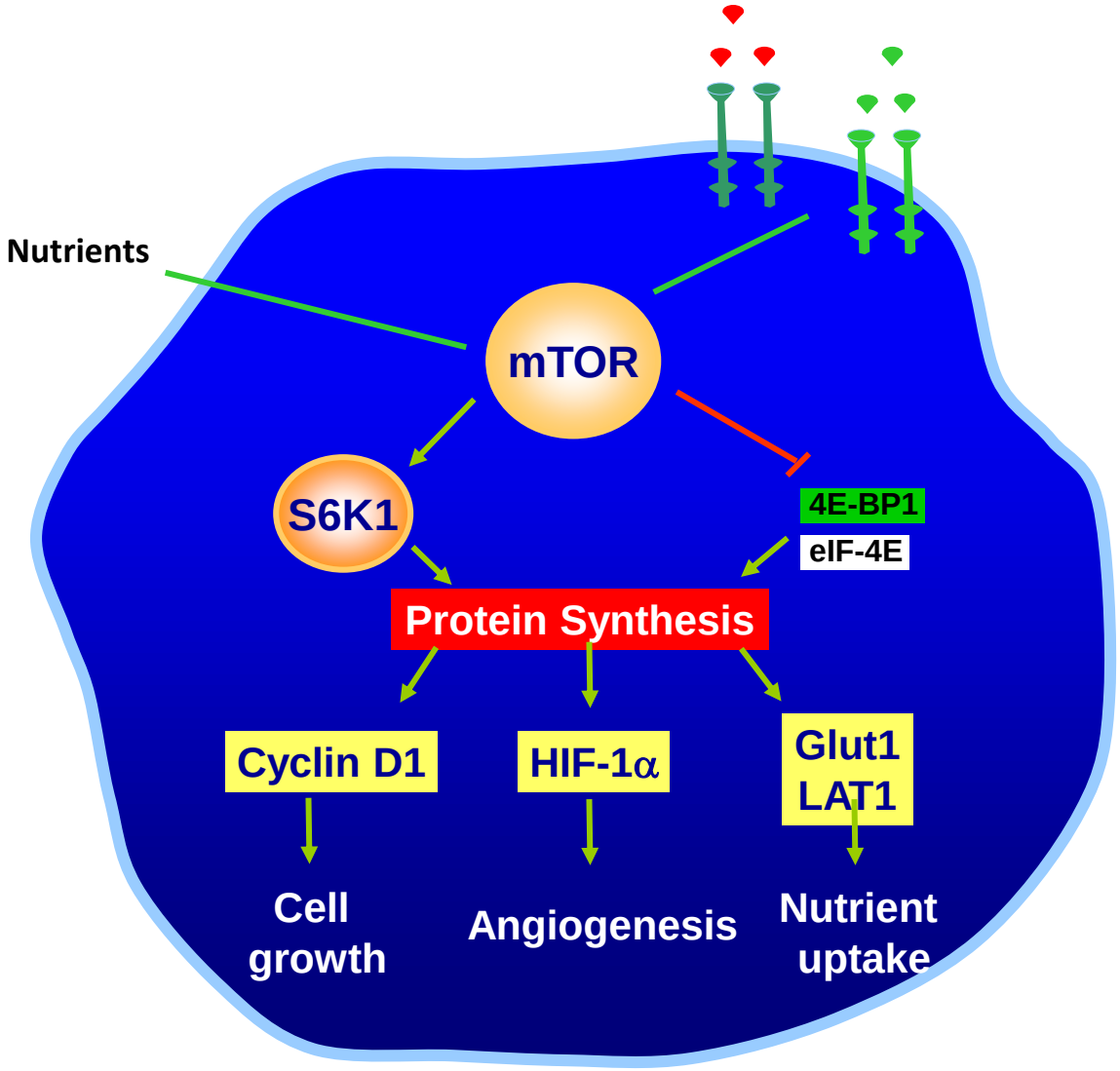
Ohsumi identified genes involved in autophagy. Alterations in these genes can occur in cancer.

The Belgian Christian de Duve was awarded the Nobel Prize for Physiology or Medicine in 1974 for the discovery of the lysosome

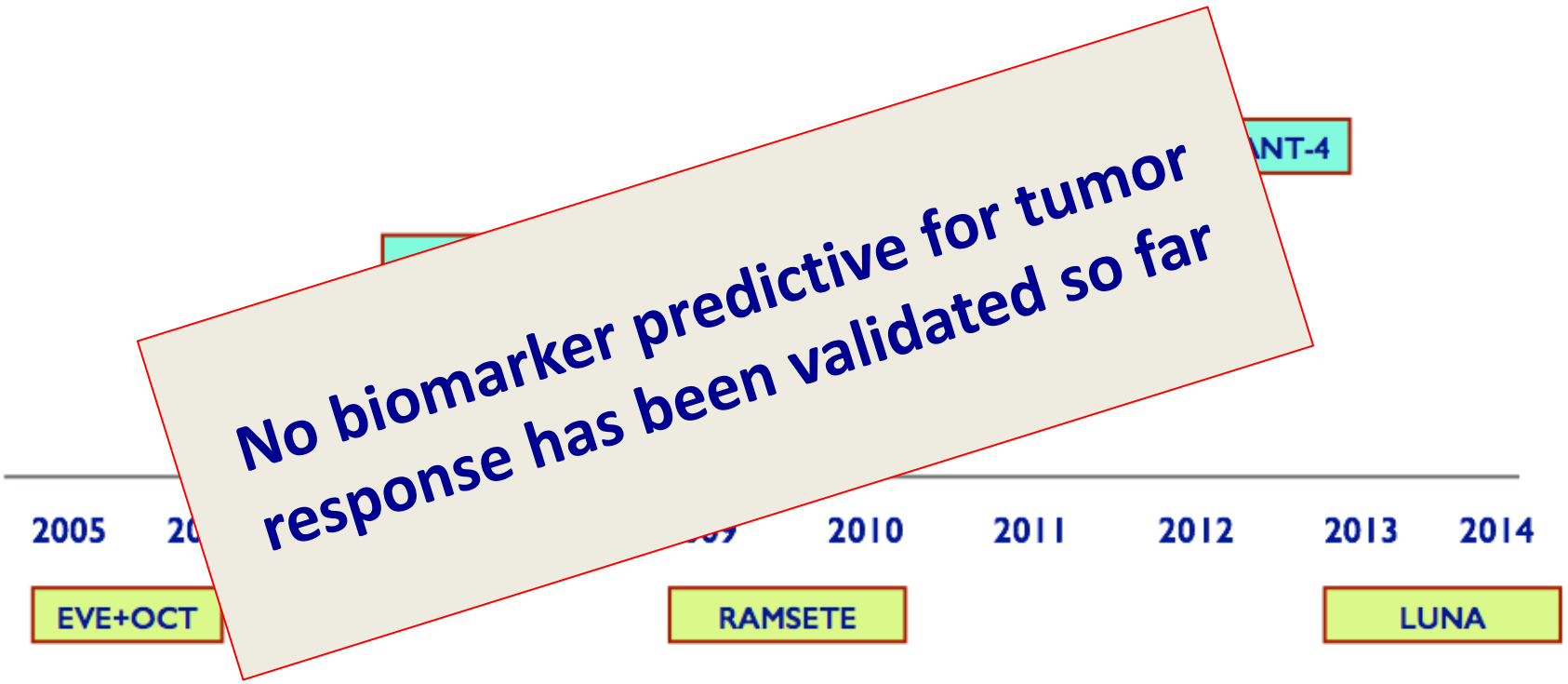
“Proteasomes” represent another cellular system to degrade the proteins (2004 Nobel Prize in Chemistry for the discovery of “ubiquitine-mediated protein degradation”)



mTOR activation supports cancer cell growth



Everolimus investigation in NETs



No biomarker predictive for tumor response has been validated so far

NIH Public Access

Author Manuscript

Anticancer Agents Med Chem. Author manuscript; available in PMC 2014 September 01.

Published in final edited form as:

Anticancer Agents Med Chem. 2013 September ; 13(7): 967–970.

Inhibition of PI3K/Akt/mTOR Signaling by Natural Products

Shile Huang*

Department of Biochemistry and Molecular Biology, Feist-Weiller Cancer Center, Louisiana State University Health Sciences Center, 1501 Kings Highway, Shreveport, LA 71130-3932, USA

Red sage

Nutraceuticals
Apigenin (flavonoid) (fruits, vegetables and beverages)
Cryptotanshinone (roots of the plant Salvia miltiorrhiza, also called red sage)
Curcumin
Fisetin (strawberries, apples, onions)
Indoles (broccoli, cauliflowers, brussels sprouts)
Isoflavones (soybeans)
Quercetin (tea, red grapes, onions)
Resveratrol (red grapes)
Tocotrienols (vit. E)

Personalized Cancer Therapy