Targeted therapies and precision oncology

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SOLVING CANCER
YOU CAN’T CURE WHAT YOU DON’T UNDERSTAND
Every person is unique. 
So is every cancer.
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.
Six Cell-autonomous mechanisms to control early oncogenesis
Somatostatin analogues: history

- 1973: Somatostatin discovery
- 1980: Development of Somatostatin analogues started
- 1987: Somatostatin receptors 1-5 were identified
- 1990: Octreotide was commercialized
- 1996: Lanreotide was commercialized
- 2004: Pasireotide introduction
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)
- Dacarbazine (DTIC)
- Temozolomide (TMZ)
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.
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.
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.
On the left side, four histological subtypes of lung cancer. On the right side, a pie chart showing the percentage distribution of molecular subsets of lung adenocarcinoma.

“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.

**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

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
Figure 5. Long-term survival in melanoma patients treated with ipilimumab: results of a pooled analysis. From [74] with permission from the American Society of Clinical Oncology.

Pennock et al., Oncologist 2015
"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

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Rapamune®</th>
<th>Certican® Afinitor®</th>
<th>Torisel®</th>
<th>Taltorvic®</th>
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<tr>
<td>Formulation</td>
<td>oral</td>
<td>oral</td>
<td>I.V.</td>
<td>I.V.</td>
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<tr>
<td>Indication</td>
<td>Prevent renal rejection</td>
<td>Prevent renal/heart rejection, NET, RCC, Breast cancer, SEGA, renal angiomyolipomas associated with TS</td>
<td>RCC, MLC</td>
<td>Soft tissue sarcoma</td>
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NET= neuroendocrine tumor; RCC = renal cell carcinoma; SEGA = subependymal giant cell astrocytoma; TS = tuberous sclerosis; I.V. = intravenous
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
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 mammals.

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
- NUTRIENTS (glucose, cholesterol, iron, zinc)
- GROWTH FACTORS (IGF, EGF, PDGF, VEGF)
- Aminoacids
- Insulin
- mTOR

- CELL GROWTH
- ANGIOGENESIS
- PROLIFERATION
- BIOENERGETICS

Barbet et al., Mol Biol Cell 1996
The pathway of mTOR

PI3K → Akt → mTORC1 → 4E-BP1 → p70S6K
mTORC2
Functions of mTORC1

PI3K

Akt

mTORC1

mTORC2

Protein synthesis

Ribosome production

Lipogenesis

Nucleotide synthesis
mTORC1 physiologically suppresses autophagy.
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
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

Nutrients

mTOR

S6K1

Cyclin D1

Cell growth

Protein Synthesis

HIF-1α

Angiogenesis

Glut1 LAT1

Nutrient uptake
Everolimus investigation in NETs

No biomarker predictive for tumor response has been validated so far
Inhibition of PI3K/Akt/mTOR Signaling by Natural Products

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<table>
<thead>
<tr>
<th>Nutraceuticals</th>
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<tbody>
<tr>
<td>Apigenin (flavonoid) (fruits, vegetables and beverages)</td>
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<tr>
<td>Cryptotanshinone (roots of the plant Salvia miltiorrhiza, also called red sage)</td>
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<tr>
<td>Curcumin</td>
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<td>Fisetin (strawberries, apples, onions)</td>
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<tr>
<td>Indoles (broccoli, cauliflowers, brussels sprouts)</td>
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<tr>
<td>Isoflavones (soybeans)</td>
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<tr>
<td>Quercetin (tea, red grapes, onions)</td>
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<tr>
<td>Resveratrol (red grapes)</td>
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<td>Tocotrienols (vit. E)</td>
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Red sage
Personalized Cancer Therapy

1. Molecular Profiling
2. Prognostic Markers
   - Markers predictive of drug sensitivity/resistance
   - Markers predictive of adverse events

Thanks!