Personalised Health Care - Cell and Gene Therapies

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Overviews

Legislation and regulations relevant to Gene and Cell therapy

- Regulatory pathway
- Applicable Divisions

Personalized Healthcare and Personalized Medicine

- CAR-T Cell Therapy
- Expedited review pathway
- Changes in drug development, science and regulations

Regulatory Challenges: Advanced Therapeutic Products

- Legislative proposals in Bill C-97

What is Gene or Cell Therapy

- **Gene therapy** is the introduction, removal, or change in the content of a person's genetic code with the goal of treating or curing a disease.
  - CAR-T cell stands for chimeric antigen receptor (CAR) T cell therapy. This a way of modifying the patient's own immune cells (T-cells) to express a receptor on their surface that recognizes structures (antigens) on the surface of malignant cells. Once the receptor binds to a tumor antigen, the T-cell is stimulated to attack the malignant cells.

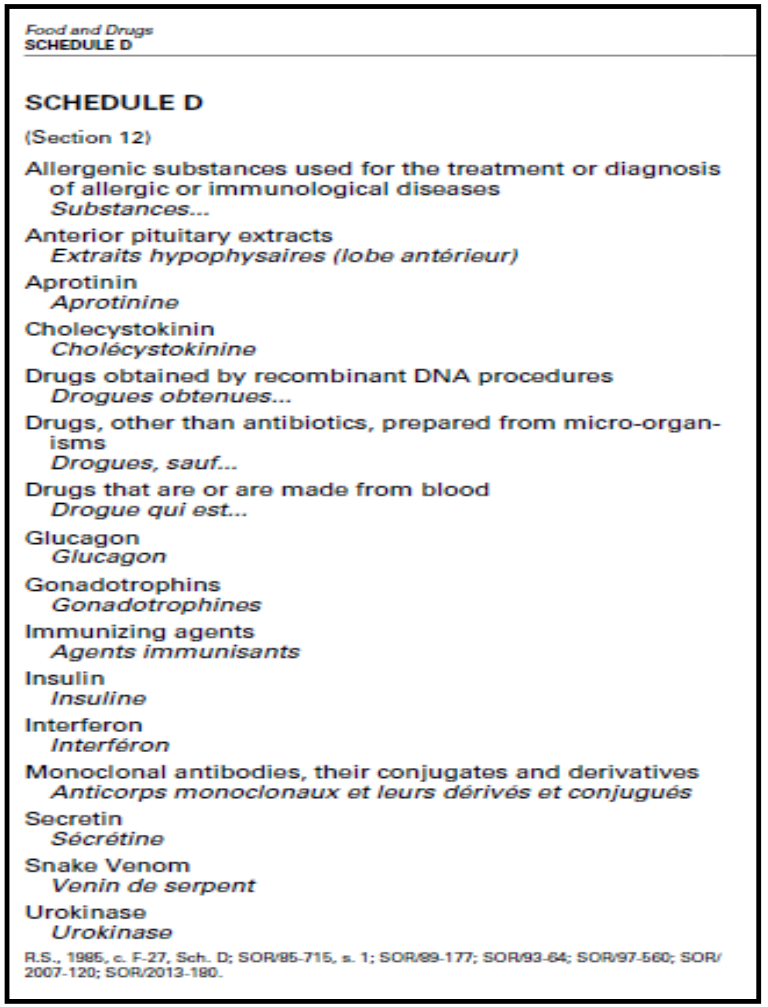
- **Cell therapy** is the transfer of intact, live cells into a patient to help lessen or cure a disease. The cells may originate from
  - A patient (autologous cells) or
  - A donor (allogeneic cells).

Gene and Cell Therapies – Biologic Drugs

- ***Food and Drugs Act*** **– does not define "biologic drug" specifically**

- **Biologic drugs are listed on *Schedule D* to the *Act***
  - **Specifically (e.g. – Insulin, aprotinin)**
  - **Within a class (e.g., Drugs that are or are made from blood; Drugs obtained by recombinant DNA technology)**

- **Generally include products derived from or through the metabolic activity of living organisms, natural or genetically modified**



Food and Drugs
SCHEDULE D

SCHEDULE D

(Section 12)

Allergenic substances used for the treatment or diagnosis of allergic or immunological diseases
Substances...

Anterior pituitary extracts
Extraits hypophysaires (lobe antérieur)

Aprotinin
Aprotinine

Cholecystokinin
Cholécystokinine

Drugs obtained by recombinant DNA procedures
Drogues obtenues...

Drugs, other than antibiotics, prepared from micro-organisms
Drogues, sauf...

Drugs that are or are made from blood
Drogue qui est...

Glucagon
Glucagon

Gonadotrophins
Gonadotrophines

Immunizing agents
Agents immunisants

Insulin
Insuline

Interferon
Interféron

Monoclonal antibodies, their conjugates and derivatives
Anticorps monoclonaux et leurs dérivés et conjugués

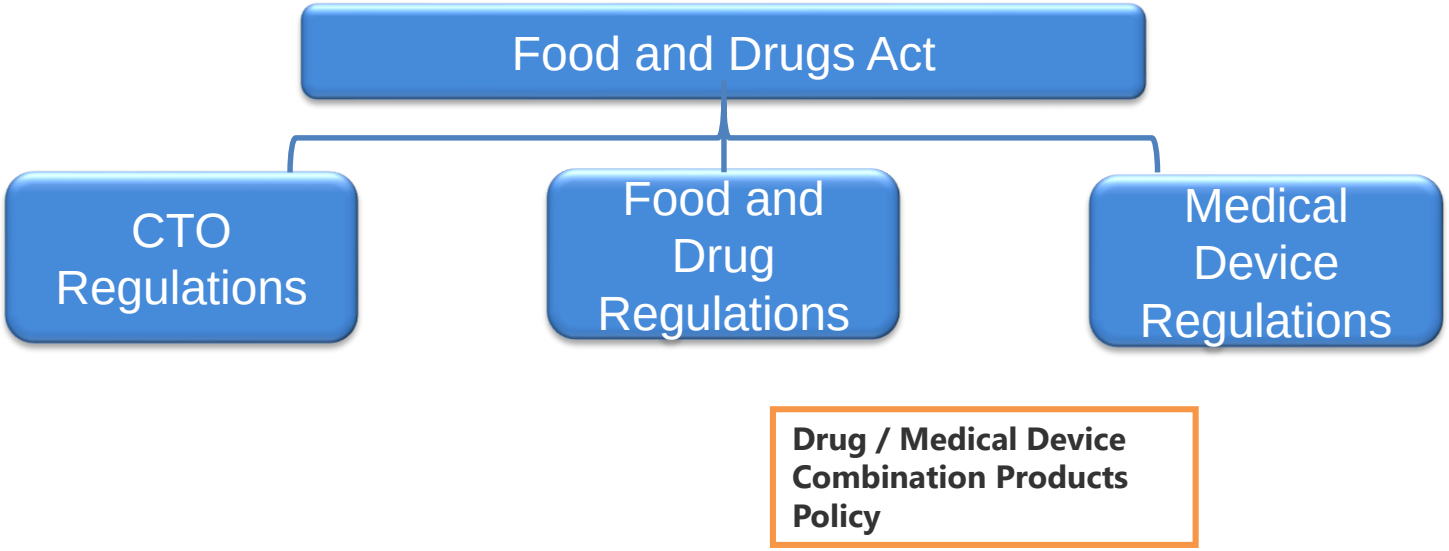
Secretin
Sécrétine

Snake Venom
Venin de serpent

Urokinase
Urokinase

R.S., 1985, c. F-27, Sch. D; SOR/85-715, s. 1; SOR/89-177; SOR/93-64; SOR/97-560; SOR/2007-120; SOR/2013-180.

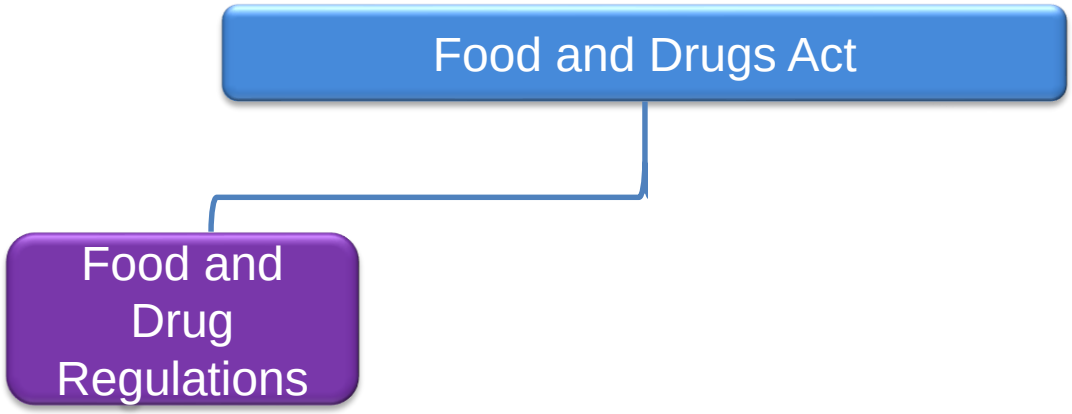
Canadian Legislation Pertinent to the Regulation of Cell and Gene Therapies



- Appropriate regulations are performance based rather than descriptive, flexible to change over time as technologies evolve, and supported by policy interpretations.

- When applied to drugs, enabling regulations find an appropriate balance:
  - They allow access to safe and effective products while prohibiting distribution of drugs manufactured under unsanitary conditions
  - They support innovation while prohibiting harmful misrepresentations

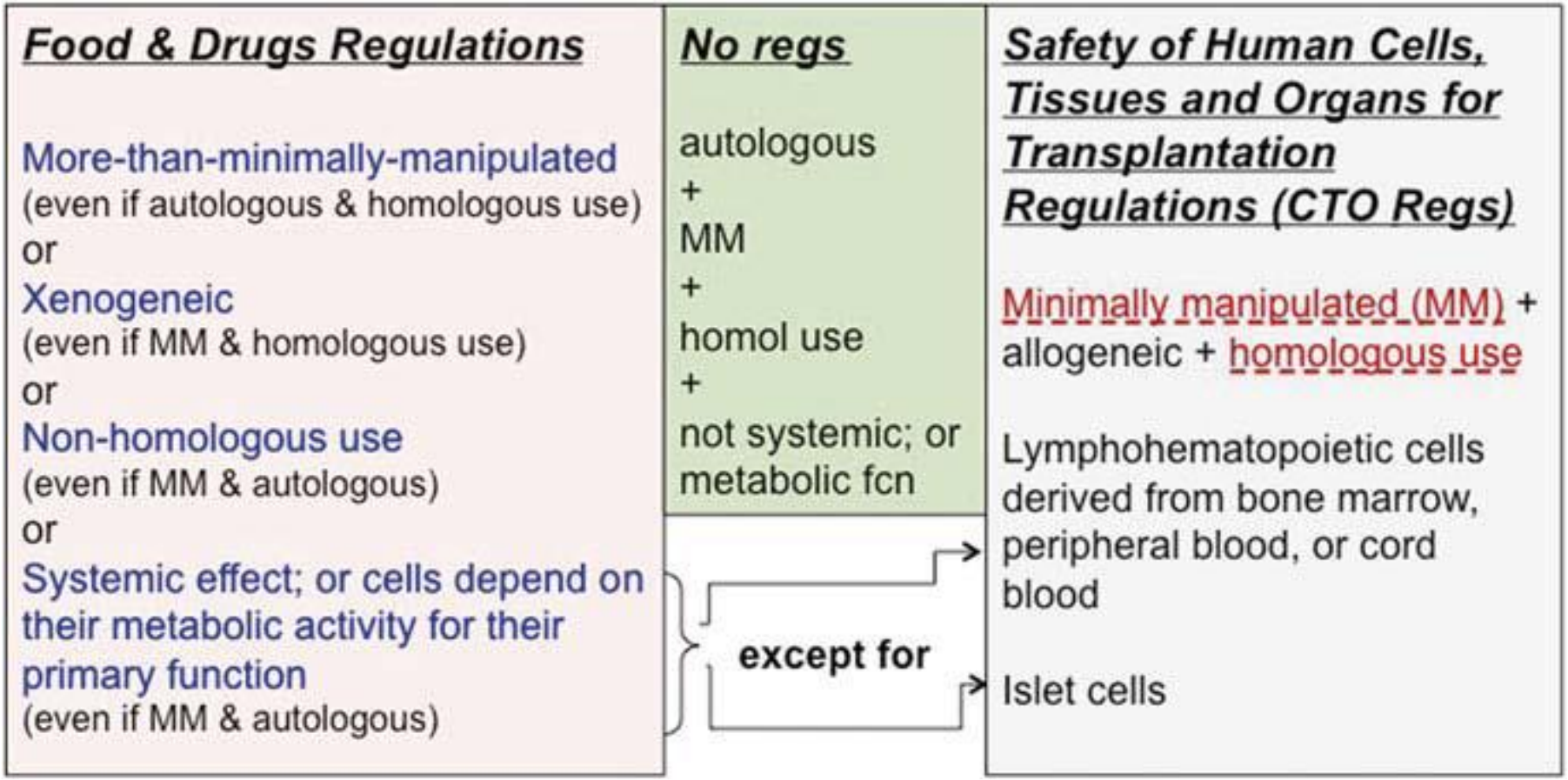
Regulatory Framework for CAR-T Therapies



Gene Therapy Definition (informal):

The introduction, removal, or change in the content of a person's genetic code with the goal of treating or curing a disease.

Regulations Governing Cell Therapies in Canada



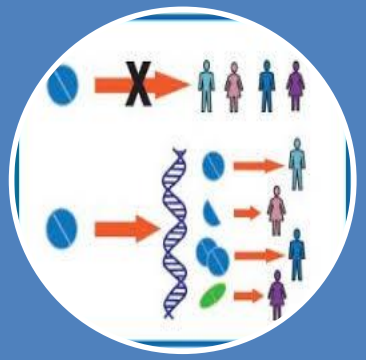
Personalized Healthcare and Personalized Medicine

- Personalized healthcare and personalized medicine are often used synonymously, but they are not exactly the same
  - **Personalized healthcare (PHC)** as a broader platform that it is an approach to the practice of medicine where prediction, prevention, intense patient engagement, shared health care decision making, and coordination of care are essential to cost effectively facilitate better outcomes.
  - **Personalized medicine (PM)** uses information of genetics and genomics of a person to prevent, diagnose and treat disease.

4Ps of Personalized Healthcare

Predictive: Identification of individual risks of developing certain diseases based on the person's genetic profile and other personal information

Preventive: Methods and treatments to avoid, reduce and monitor the risk of developing certain diseases



Personalized: Clinical interventions based on the unique genetic, medical and environmental characteristics of each patient, and genomic profile of his/her diseases

Participatory: Patients are fully engaged in personal health management

Personalized Medicine Are Used To

Personalized: Clinical interventions based on the unique genetic, medical and environmental characteristics of each patient, and genomic profile of his/her diseases

help patients with cancer make treatment decisions that are right for them

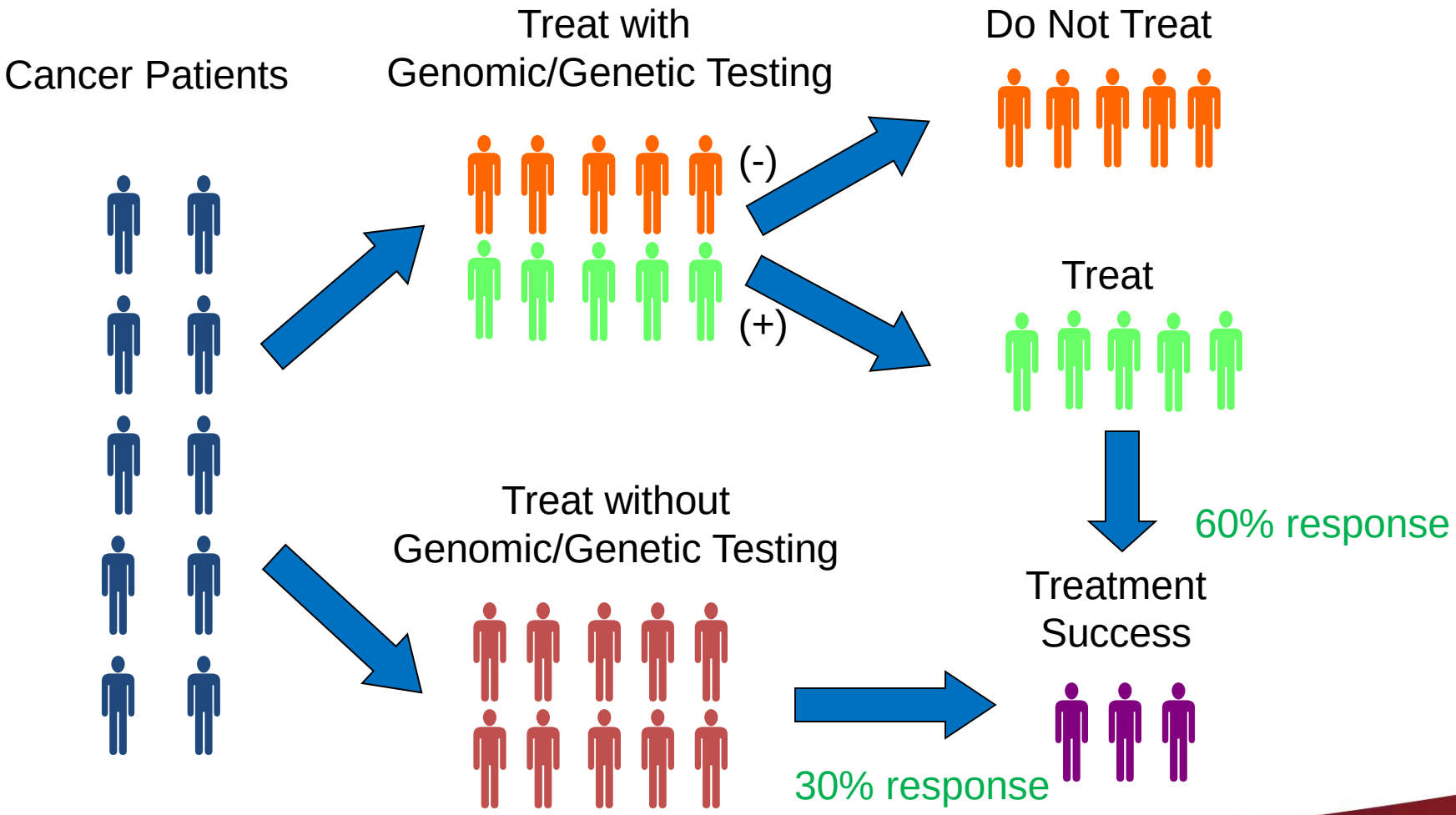
- select who may benefit from earlier screening or tests to find cancer early
- match a person to treatments that are more likely to work while causing fewer adverse events
- be custom-made for each patient (T-cell/stem cell/NK cell etc.)
- plan and monitor treatment

History of Personalized Medicine

Personalized medicine is an emerging field, but the logic behind it is old.

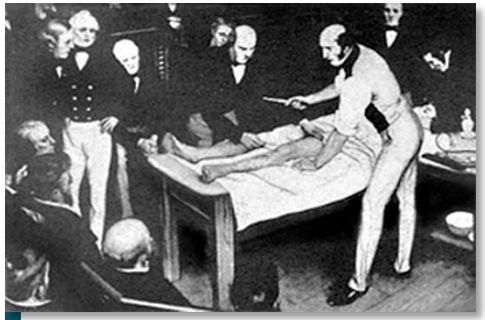
- In the past, doctors used:
  - Family history
  - Socioeconomic circumstances
  - Environmental factors
- Now:
  - genomic/genetic testing
  - proteomic profiling
  - Companion decision tools to guide treatment
  - AI techniques that uncover complex associations from accessing a large volume of data

Personalized Medicine Reduces Ineffective Treatment in Cancer



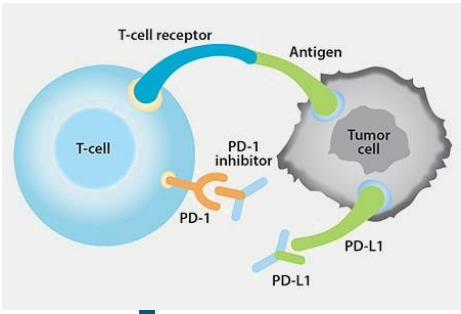
Evolution of Cancer Therapy: Treatment Modalities

Screening patients with genomic/genetic testing



Surgery
1846

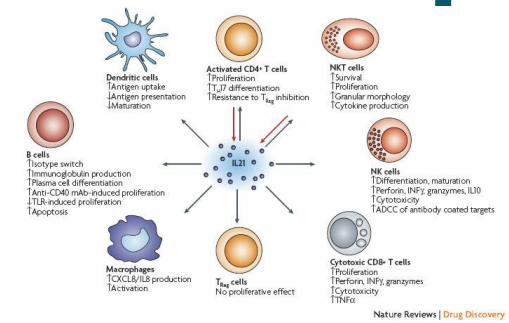
Chemotherapy
1946



Immuno-oncology (IO)
Sipuleucel-T 2010
Ipilimumab 2011

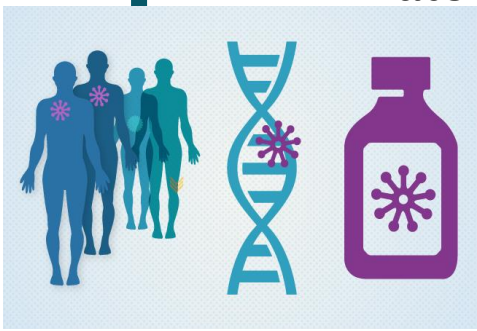
Radiation Therapy
1901

Immunotherapy
Interferon-α 1995
Interleukin-2 1998



Targeted Therapy
1997

ibs mabs



Rise of Cell-based Immuno-oncology

- Game-changing discoveries – more coming for Personalized medicine

2011

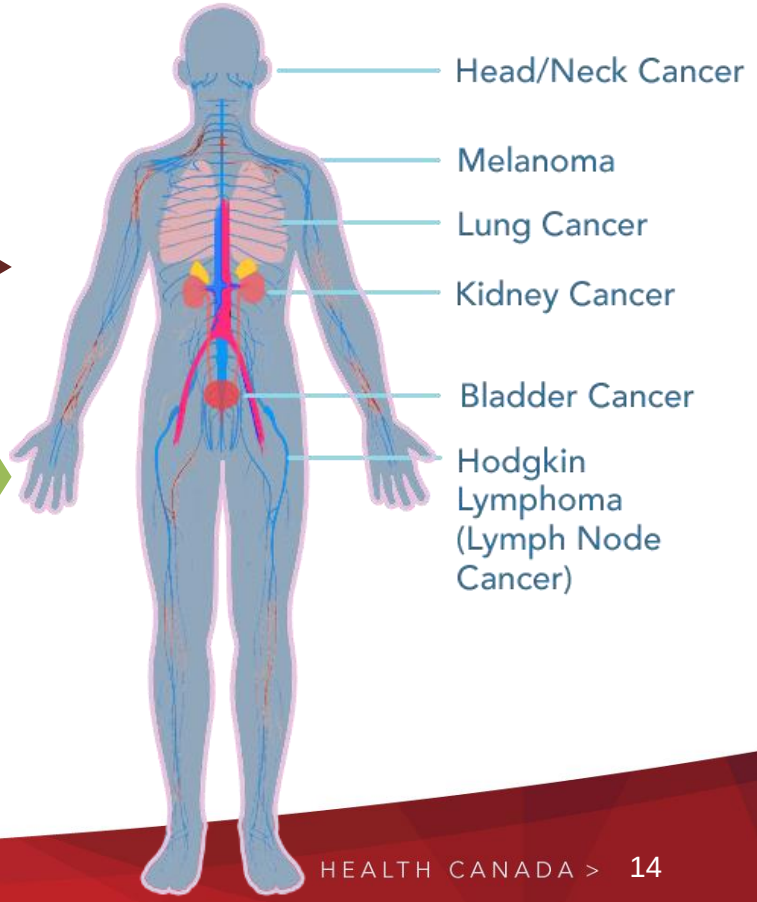
Ipilimumab introduced for melanoma

2014

Pembrolizumab, nivolumab approved for melanoma

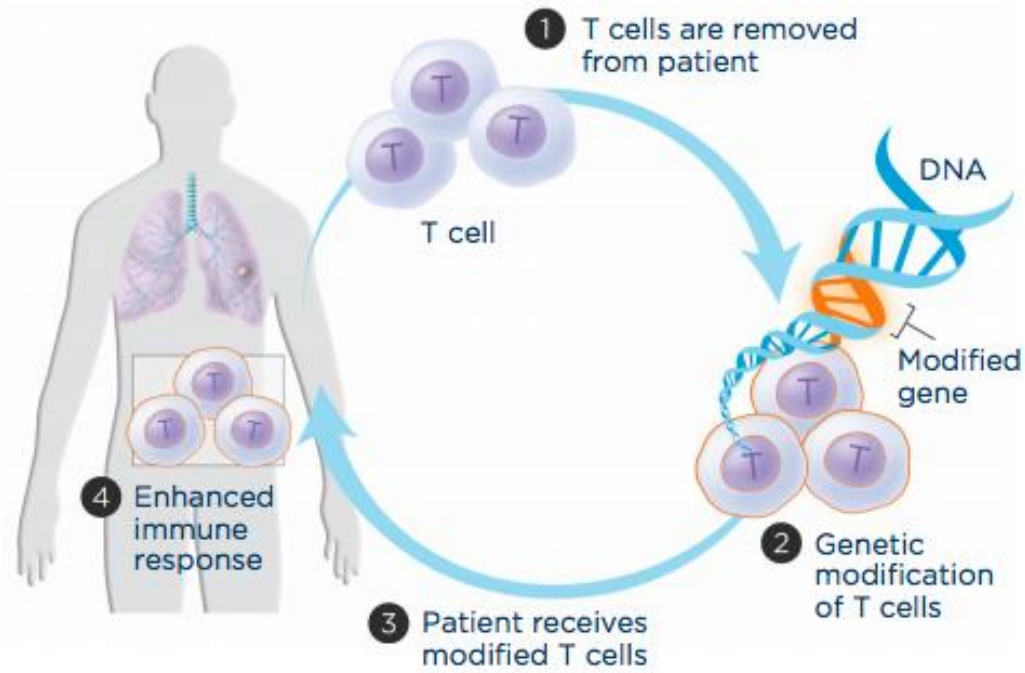
2017

CAR-T cell therapy for acute lymphoblastic leukemia (ALL).

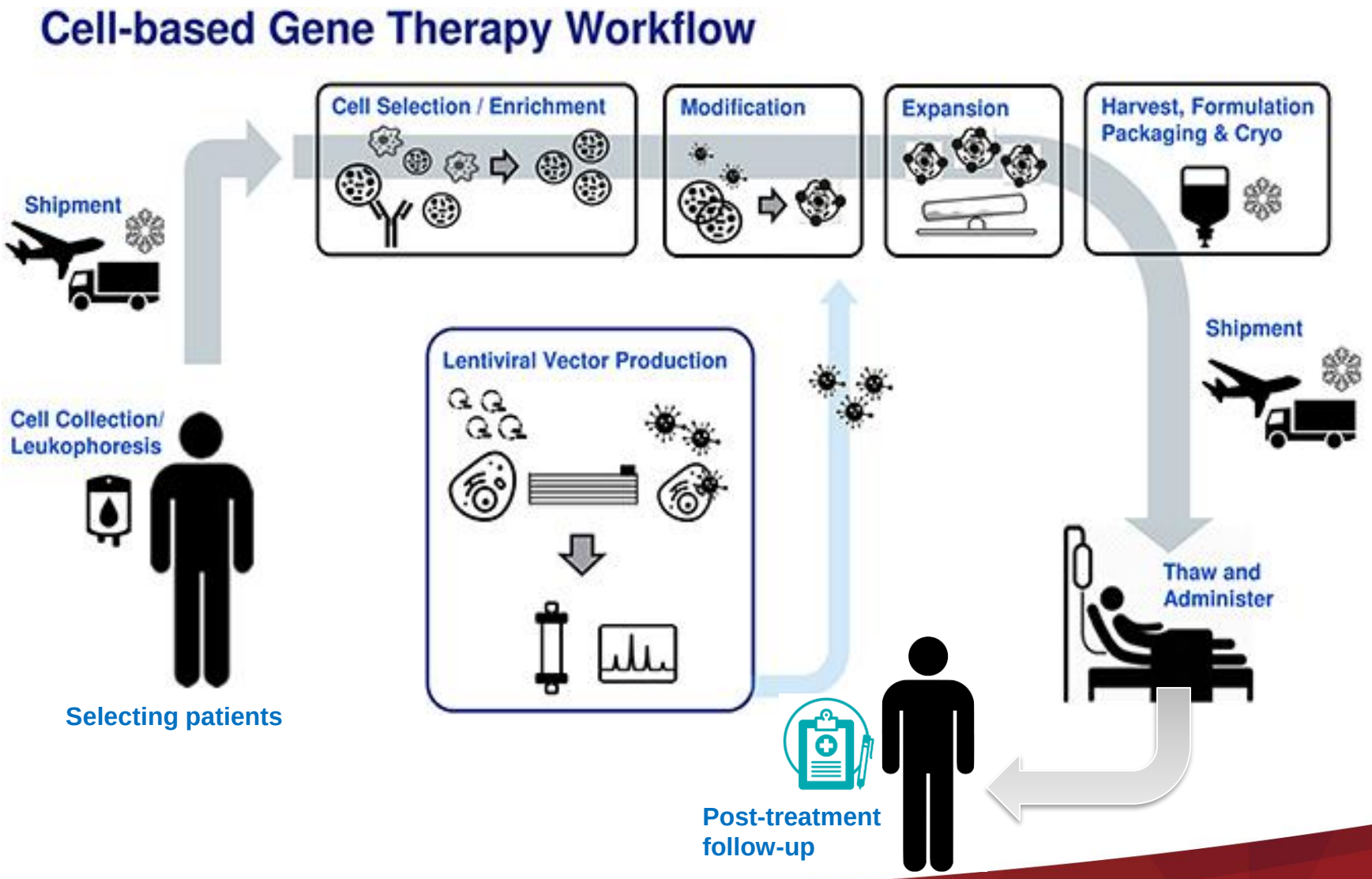


Taking Personalized Medicine to a New Level: CAR-T Cell Therapy

- Known as CAR-T therapy, the treatment involves genetically altering a patient's T-cells with chimeric antigen receptors (CARs) that can find and destroy cancer cells that normal T-cells wouldn't be able to detect.
- Once in the bloodstream, CAR T-cells continue to multiply, making the CAR-T therapy a living drug.



Process of CAR-T Therapy: A Case of Personalized Healthcare



Gene and Cell Therapy Authorized in Canada

CAR-T cell Therapy: A New Era in Cancer Immunotherapy

- **Kymriah (Tisagenlecleucel)** is authorized to treat adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and for children and young adults (ages three to 25) with relapsed or refractory acute lymphocytic leukemia (ALL). (NOC date: Sep 6, 2018)
- **Yescarta (Axicabtagene Ciloleucel)** is authorized for the treatment of adult patients with relapsed or refractory large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy. (NOC date: Feb 24, 2019)

Canada is the first country to authorize a stem cell therapy

- **Prochymal** is authorized for treatment of graft-versus-host disease (GVHD), in children under 18 under Health Canada's Notice of Compliance with conditions (NOC/c). (NOC/c date: May 18, 2012)

Expedited Review: Priority Review Pathway and NOC/c

- Both Kymriah and Yescarta have been qualified for **Priority Review status** and were reviewed in **180 days rather than the standard 300 days.**
- Advanced consideration for a **Notice of Compliance with Conditions** would also be applicable to gene and cell therapies
  - NOC/c clinical eligibility criteria are in line with Priority Review criteria, but applies to products with promising evidence of clinical efficacy **(review time: 200 days)**.

Canadian Health Systems Are Changing (2018)

Data

Data-generating and data-reliant systems for all aspects of health

Citizen Agency

Information and resources to manage individual care

Precision & Personalization

Individualization of systems and services

Product Complexity

Innovations that blur product lines and defy standard classification

Production & Distribution

Local, connected, and accountable manufacturing and supply chains

Evidentiary Standards

New technologies, R&D practices, and trial designs challenge review processes

Accelerated Review Proposal under R2D2

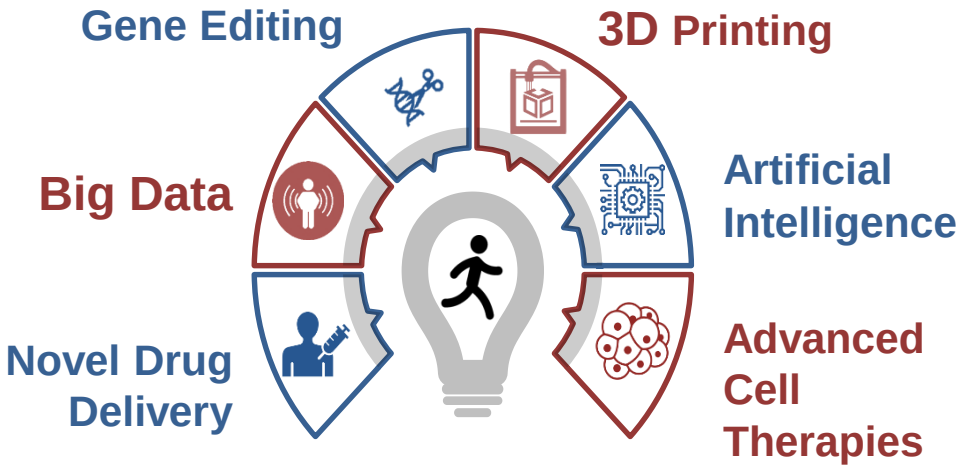
A new accelerated review pathway is proposed and posted for consultations now. The revised guidance document proposes the following:

- Maintaining the overarching principle that the drugs being accelerated are those for serious and life-threatening conditions
- Combining priority review and NOC/c into a single pathway – allowing first an assessment of whether the product is qualified for an accelerated review, and a later decision about whether the available evidence supports a standard NOC, or NOC/c
- Adding more clarity that the types of drugs being accelerated could include products that reduce patient burden or meet departmental and public health priorities, and identifying specific underserved populations of note, including pediatrics and rare diseases
- Allowing a limited amount of competitors to also be eligible for accelerated review – within a year of the first marketing, to support availability of alternatives and the system in a way that might support affordability

Link to the draft document https://www.canada.ca/en/health-canada/programs/consultation-draft-guidance-accelerated-review-human-drug-submissions.html

Regulatory Challenges: Advanced Therapeutic Products (2019)

- The speed at which innovative products can be developed, the method with which they are made or distributed, and how data can be collected, has resulted in a shift away from the traditional product development model for which the current regulations are based
- Some health products are so novel and distinct that it is difficult for them to meet the current regulatory requirements
- Lack of appropriate regulatory oversight for continuously changing products and innovative business practices



Legislative Proposals in Bill C-97

- It includes proposed amendments to the Food and Drugs Act to introduce a new framework for a new class of therapeutic products called "advanced therapeutic products" that will be contained in Schedule "G".
- Products in this category will represent an emerging or innovative technological, scientific or medical development.
- Advanced therapeutic products will require authorizations (by license or ministerial order) before they can be imported, sold, manufactured, prepared, preserved, packaged, labelled, stored, or tested.

Flexible and Risk-based Oversight for Clinical Trials

- The randomized controlled trial has been the gold standard for establishing standard treatments.
- Personalised medicines/advanced therapies are often developed for rare and previously untreated diseases, which may have limited the feasibility of conducting randomized controlled trials.
- New experimental designs and methods of data analysis have been developed, for example, the group sequential design, sample size re-estimation, and adaptive designs, such as the seamless phase II/III design.
- In oncology, new clinical trials that use basket, umbrella, platform, or other master protocols are expected to increase due to the focus on genomic medicine.
- Health Canada recognise that these changes require a different approach towards benefit-risk analysis. Randomised Phase III trials are not always ethical or feasible when developing drugs for treatment of small populations.
- Alternative strategies comprise expedited authorization via NOC/c, which can be granted based on small non-randomised Phase II trials.

Changing Clinical/Scientific Environment at Pre-Market

Gene, cell and other advanced therapies may pose concerns

- some truly ‘personalized’
- single arm study
- small patient numbers
- unique pharmacokinetic profile
- right dose for cell and gene therapies
- the possibility of prolonged biological activity
- high potential for inducing immunogenicity
- long observation periods for benefit-risk assessment
- combinatorial complexity of possible combination therapies
- clinical indication difficult to define

Health Canada's Evolving Approach to Leveraging Information and Resource for Marketing Decisions and Drug Access

We hold pre-submission meetings and provide feedback to sponsors in terms of data acceptability and filling strategies.

We seek to increase our understanding of genomic/genetic/biomarker testing and pharmacometrics data used in innovative medicine development, and maximise the benefit of innovative medicines to the patients.

We are working to optimize the use of Real World Evidence (RWE) for regulatory decisions in order to improve the extent and rate of access to prescription drugs in Canada.

We engage in bilateral or multilateral discussions or collaborations with our international counterparts (FDA, EMA, TGA, etc.) and use foreign reviews to enhance the decision-making process.

Health Canada, CADTH and INESSS collaborate to Align Drug Review Processes in order to reduce the time between market authorization and reimbursement recommendations for public drug plans.

Conclusions

- Personalized medicine has the potential to change the way we think about, identify and manage health problems.
- It is already having an exciting impact on both regulatory decision and patient care.
- This impact will grow as more advanced medicines in the current drug development pipeline coming to market.
- Health Canada is adopting flexible regulatory approaches to address these challenges

Thank you

Merci

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