Re-thinking Comparability Assessments for Individualized Therapeutics

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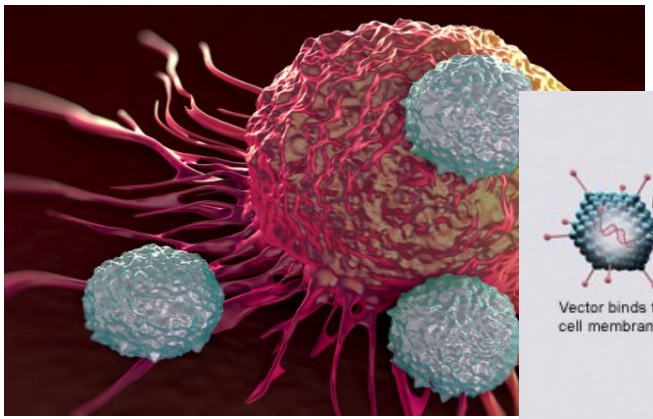
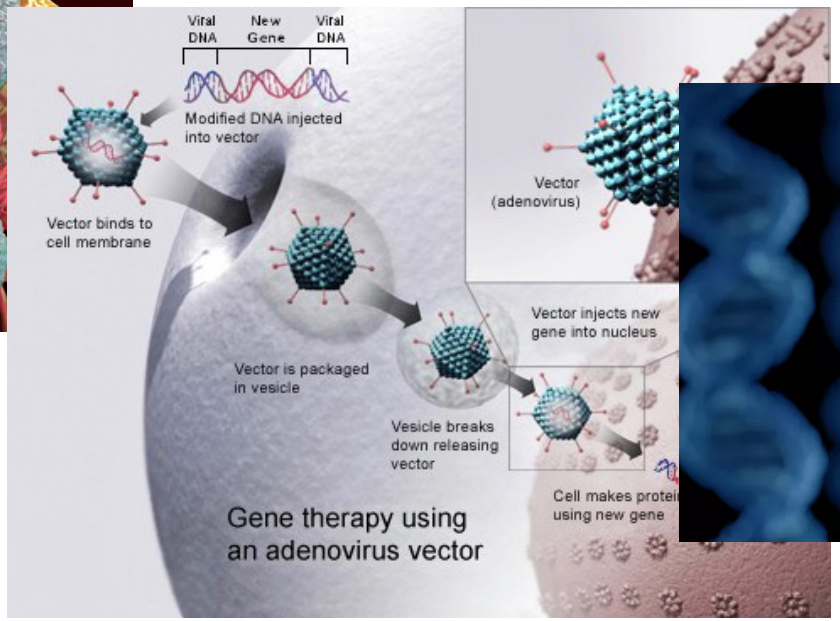
Cell and gene therapies include a wide variety of product platforms

Examples include…

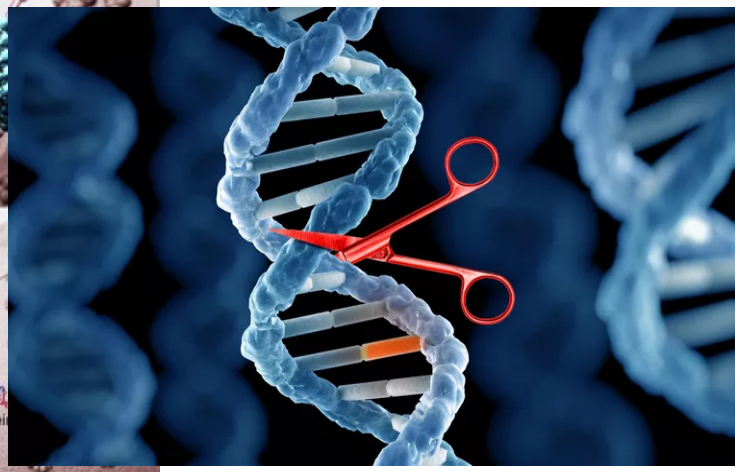
Cell-based Therapeutics



Gene Therapy Products



Gene Editing

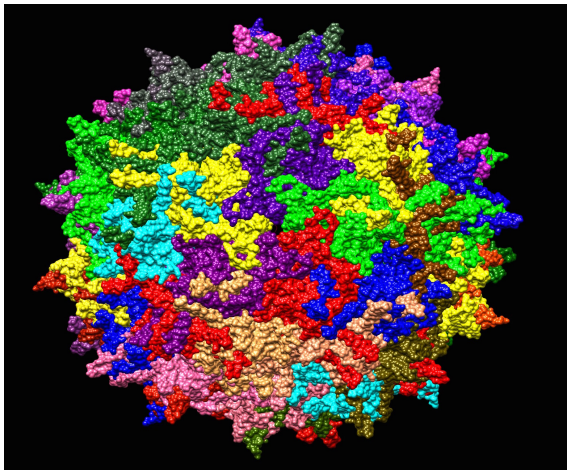


Gene therapies with viral vectors

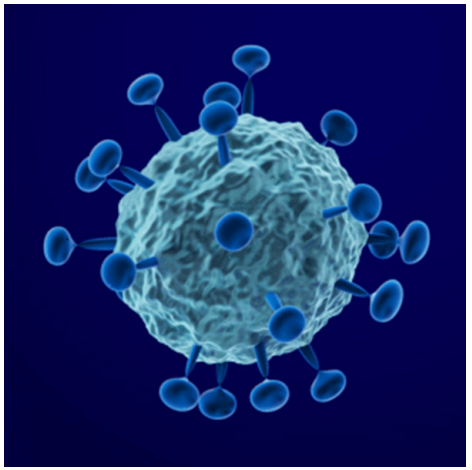
There are two main viral vectors used for gene therapies currently. They are:

AAV (adeno-associated virus): a small virus that infects humans but is not known to cause any disease. It is a small (20 nm), replication-defective, non-enveloped virus.

LV (lenti virus): a spherical enveloped retrovirus (80-100 nm). It can cause chronic and deadly diseases characterized by long incubation periods (most common HIV). It can integrate a large amount of cDNA into the host.



Adeno-associated Virus (AAV)



Lentivirus (LV)

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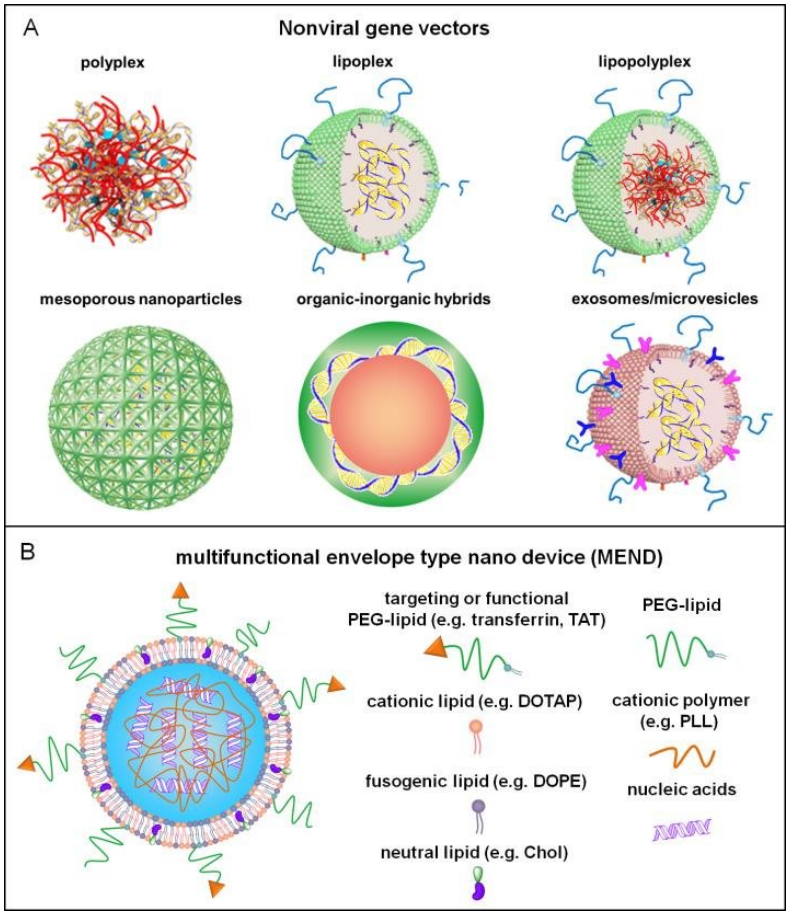
Gene therapies with non-viral vector systems



Nucleic acids: DNA and RNA

Liposomal formulations:
To protect the nucleic acid.
Can be made of lipids in an organized structure, like micelle or liposome

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Cell and gene therapy products can be fundamentally different than conventional medicinal products

- Some of them are individualized (made-to-order for a single patient) while others are produced for a group of patients
- Some require human tissue samples for their production, and others do not
- Some of them have unintended, but inherent variability while others have intended variability by design (e.g. individualized neoantigen-specific therapies (iNeST))
- Different platforms of cell and gene therapy products have different challenges and requirements

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The rate of change is so fast that regulations struggle to keep up with technology

- "Without clear knowledge of the future potential or future unintended negative consequences of new technologies, it is nearly impossible to draft regulations that will promote important advances – while still protecting ourselves from every bad side effect."
  - --Thomas Friedman (from "**Thanks for Being Late**: An Optimist's Guide to Thriving in the Age of Accelerations")

- The rapid pace of innovation and technological advances – requires rapid and focused development of solutions to move beyond old systems and ensure that appropriate patients can benefit from this new frontier of medicines…

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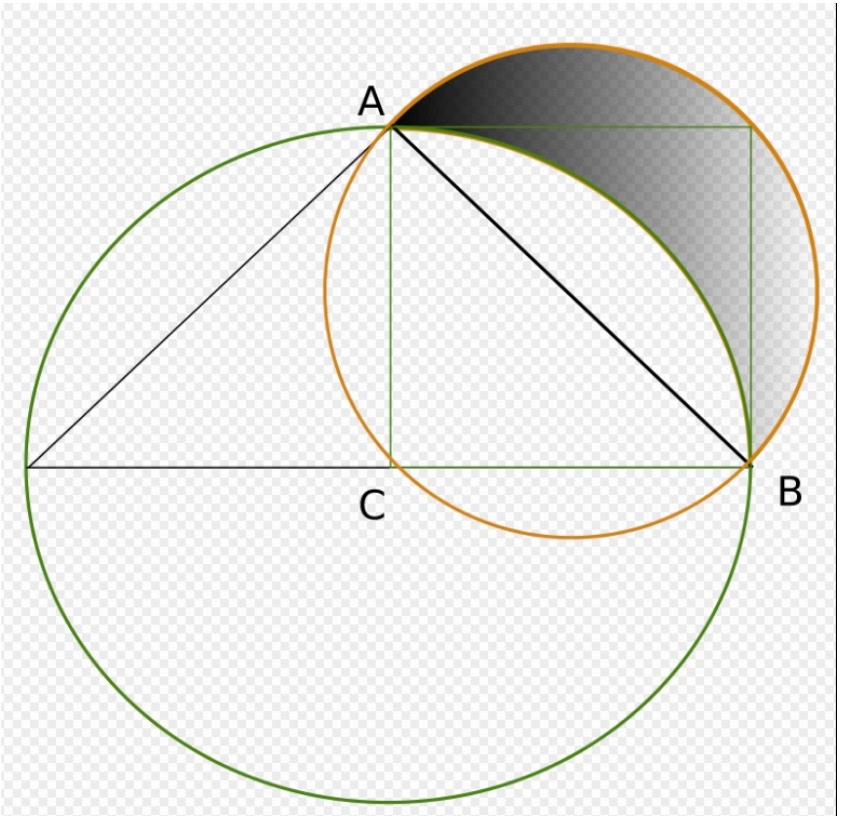
Next generation medicines: Are we trying to fit square pegs into round holes?

Existing regulations were established for traditional medicinal products (small molecules and biologics)
-To apply them to new modalities, need **flexibility** (not leniency), so developers focus on *appropriate* controls

Some regulatory guidelines have served the biotech field well, and should be **adapted**

But in some cases, **novel** approaches are needed.
-Manufacturers need a different mindset and need to work with regulators to re-write the rules



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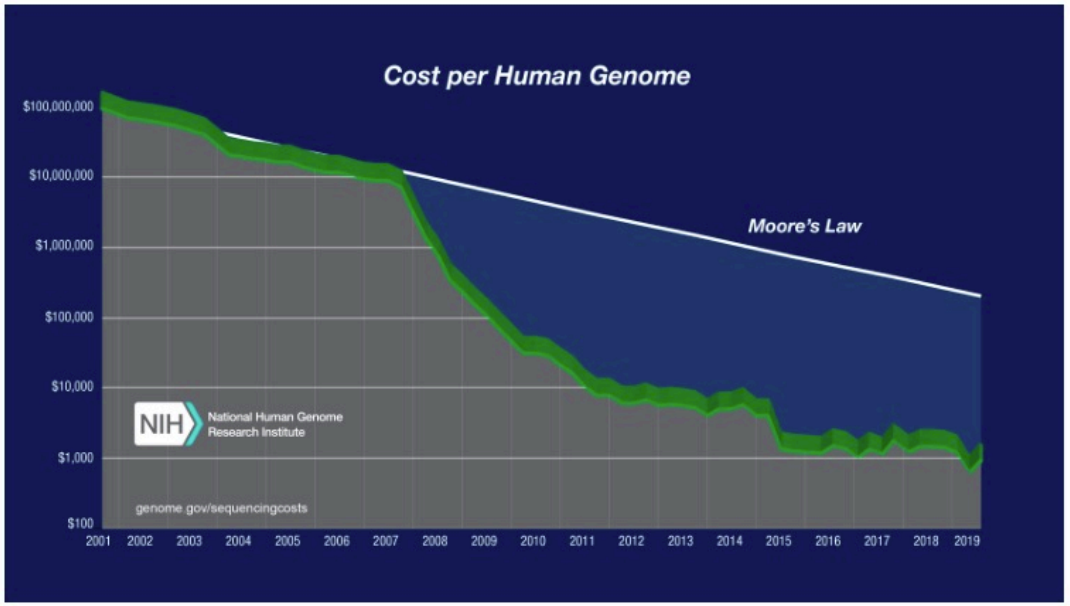
Example: Rapid and profound evolution in genome sequencing

The cost of sequencing the first whole human genome was about $2.7 billion in 2003 and took ~13 years to complete.

The cost decreased to about $1,000-3,000 in 2016 and takes one or two days.

* Many factors go into determining the cost of sequencing a genome.



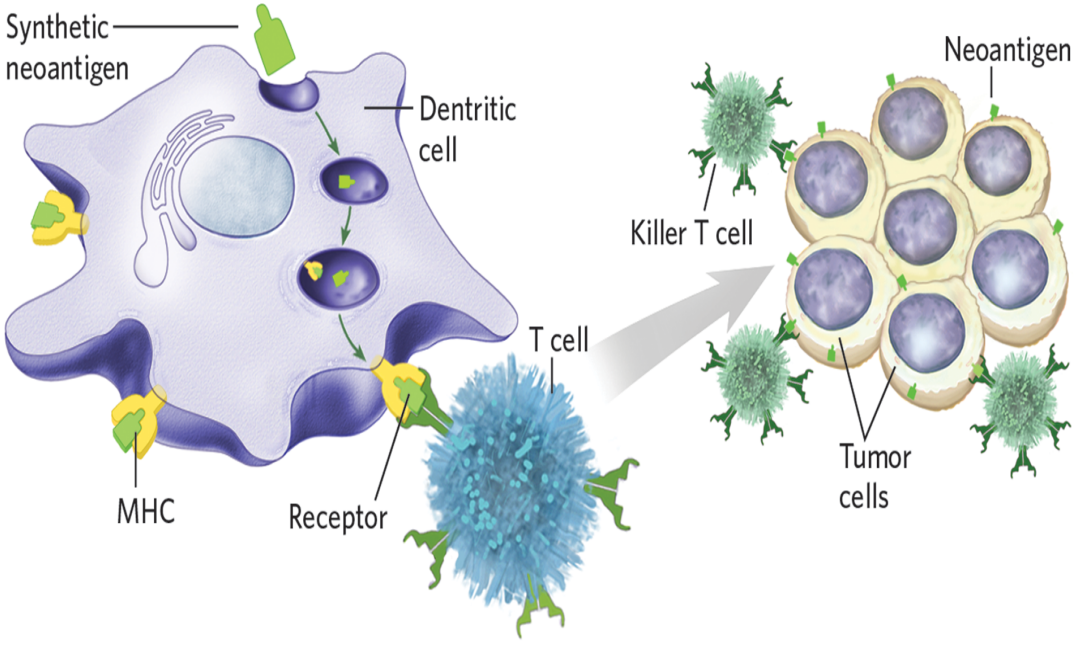
Cost per genome data

Advances in sequencing technology enabled neoantigen specific therapies

Neoantigen-specific immunotherapies (NeST) (also known as ‘cancer vaccines’) seek to mount a natural immune response to a cancer-specific (neo)antigen.

NeST can be cell-, protein-, or nucleic acid-based products

NeST ultimately deliver the neoantigen peptides that will activate a cell-mediated immune response.



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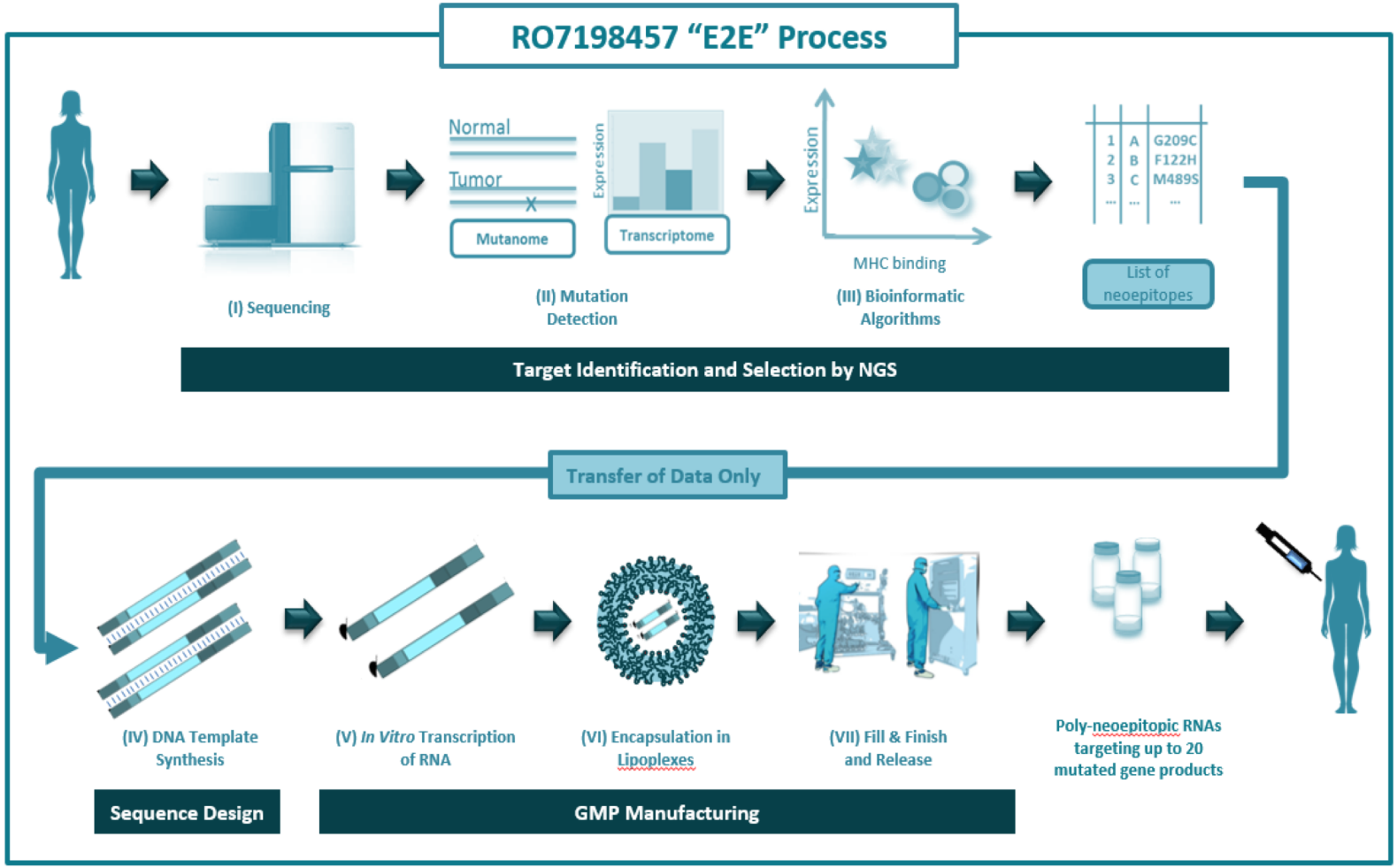
Individualized NeST (iNeST): End-to-End Production Process



Changes in neoepitope selection process evaluated at process level (not product)

Changes in DS and/or DP process evaluated at product level with pairwise comparisons

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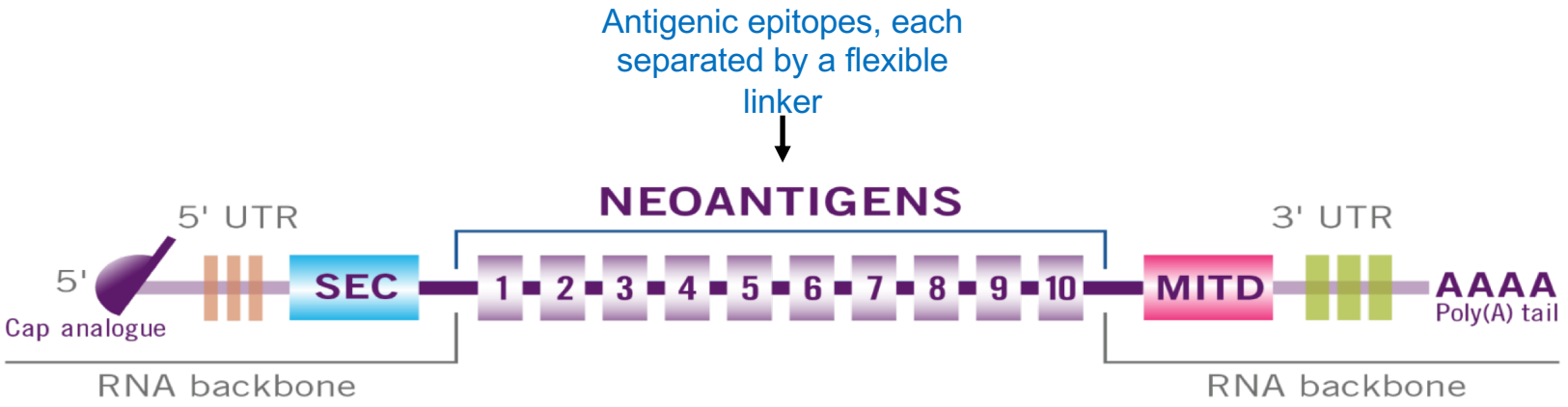
iNeST: Final product is messenger RNA (mRNA)



- iNeST mRNA is engineered to elicit CD4 and CD8 immune responses to multiple patient-specific neoantigens
- Each patient's mRNA is unique in the neoantigen cassette region.
- Total length of mRNA may vary but is generally on the order of ~2000 nucleotides

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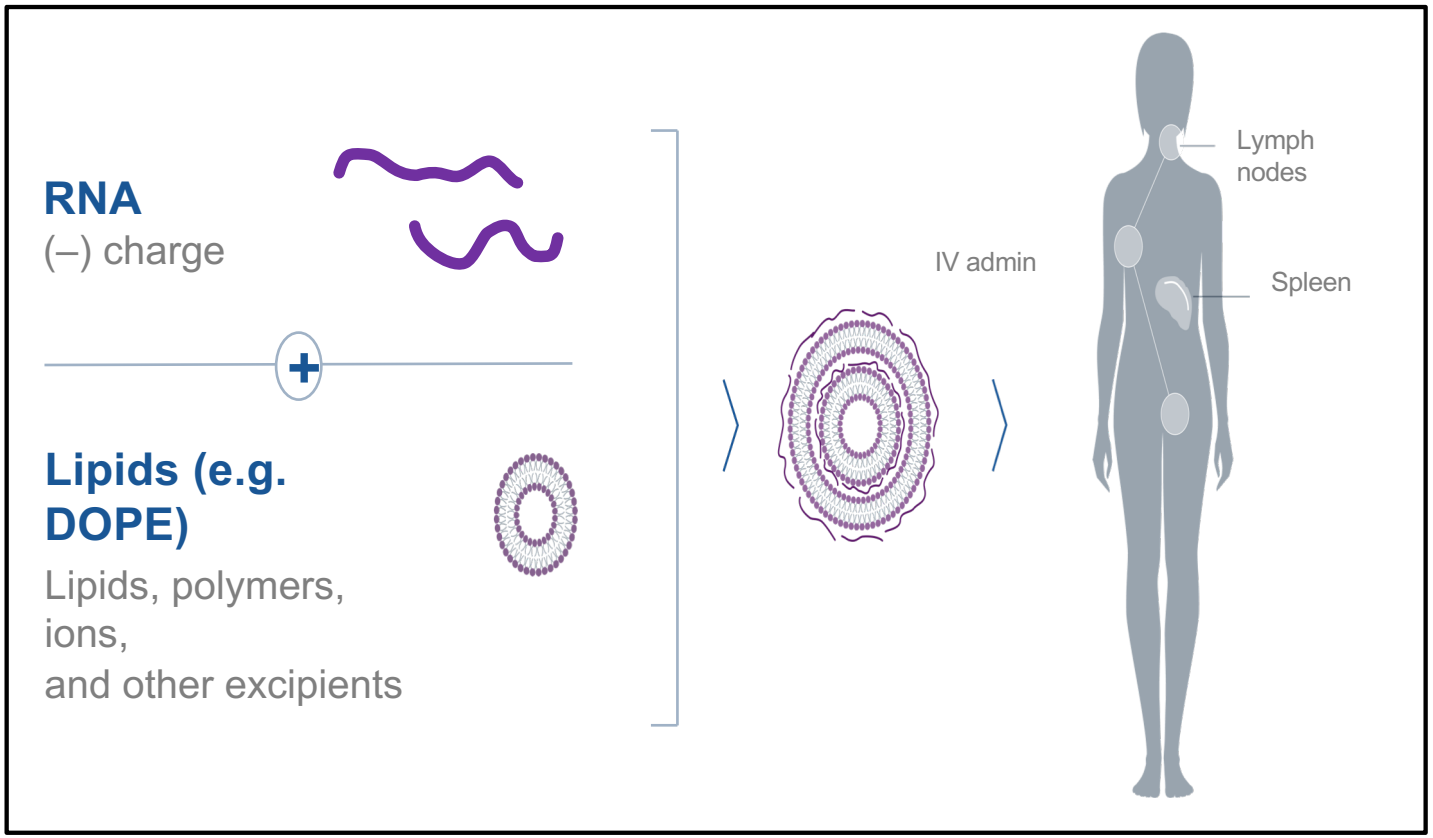
Liposomal formulations protect mRNA and enable systemic administration

Lipid-to-mRNA ratio affects uptake by cells – example for intravenous administration



Synthetic and naturally occurring lipids are used in liposome formulations

Lipid nanoparticle protects mRNA from nucleases in the blood while distributing to, for example, lymphatic compartments

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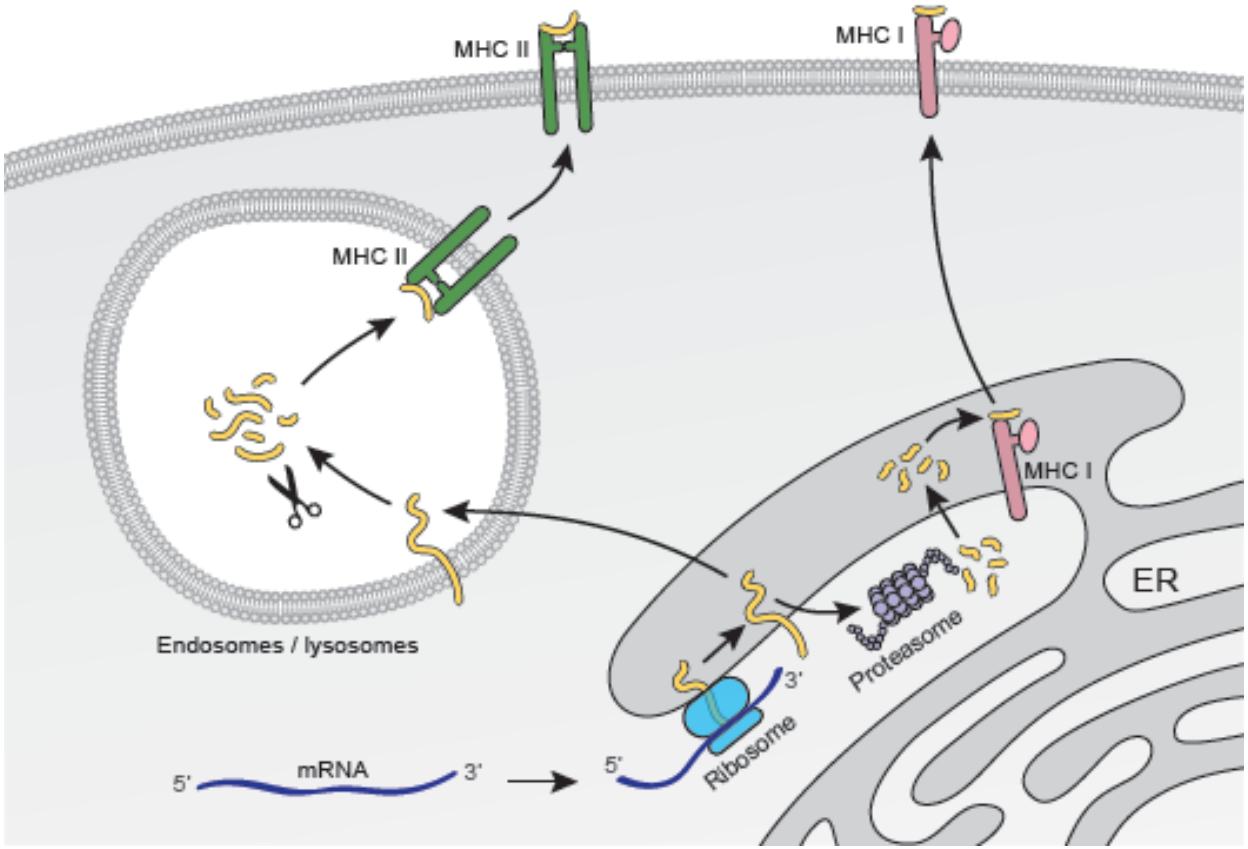
Immunogenic neoantigens result from processed and presented mutant peptide sequences recognized by T cell receptors



antigen-presenting cell

- Induction and expansion of antigen-specific $CD8^+$ and $CD4^+$ T cells (via epitopes presented on MHC class I and II complexes, respectively)
- Systemic distribution
- Anti-tumoral effect

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RNA and RNA-lipoplex manufacturing process updates

Comparability assessments applying principles from ICH Q5E can be conducted, with some adaptation, to evaluate such manufacturing process changes

- Manufacturing Processes:
  - mRNA produced by in vitro transcription (IVT) in cell-free, enzymatic process
  - RNA-lipoplex produced by formulation with liposomes
- The RNA and RNA-lipoplex are relatively well characterized analytically, which is required for meaningful analytical comparison of pre- and post-change product
- Since each patient's batch has unique properties, need pairwise comparisons of batches.

Addition of new GMP manufacturing facility: Split the manufacturing stream from starting material (DNA template) to produce a pair of batches, which can then be compared head-to-head

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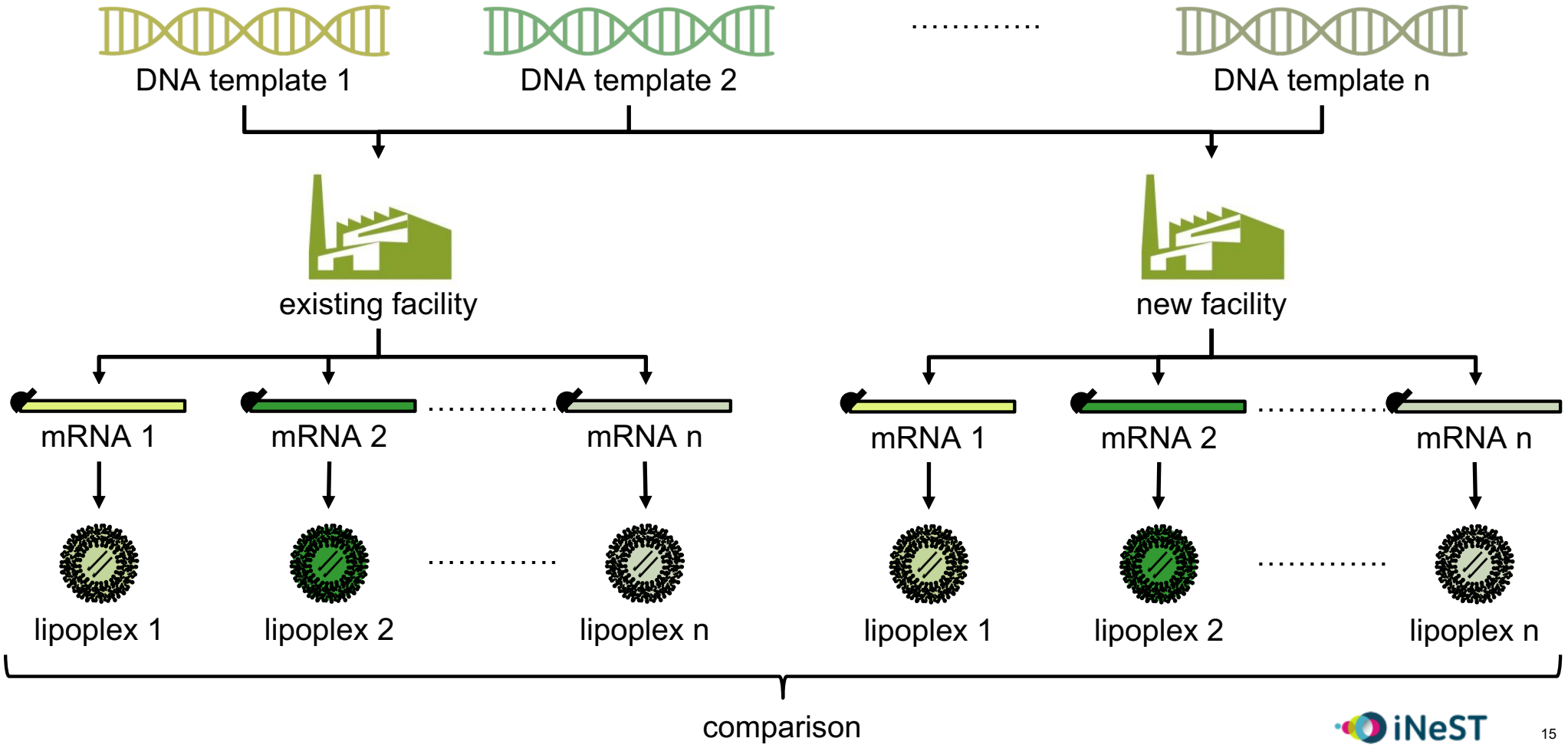
Split-stream manufacturing: Pairwise comparison of batches



DNA template reference sequences

- Design a set of sequences that encompasses the space of potential patient-specific sequences (including worst case and best case scenarios as well as typical sequences)
- Factors to take into considerations might include:
  - Sequence length (defined by number and length of individual neoepitopes)
  - GC-content (due to amino acid [and thus the corresponding codon triplet] distribution)

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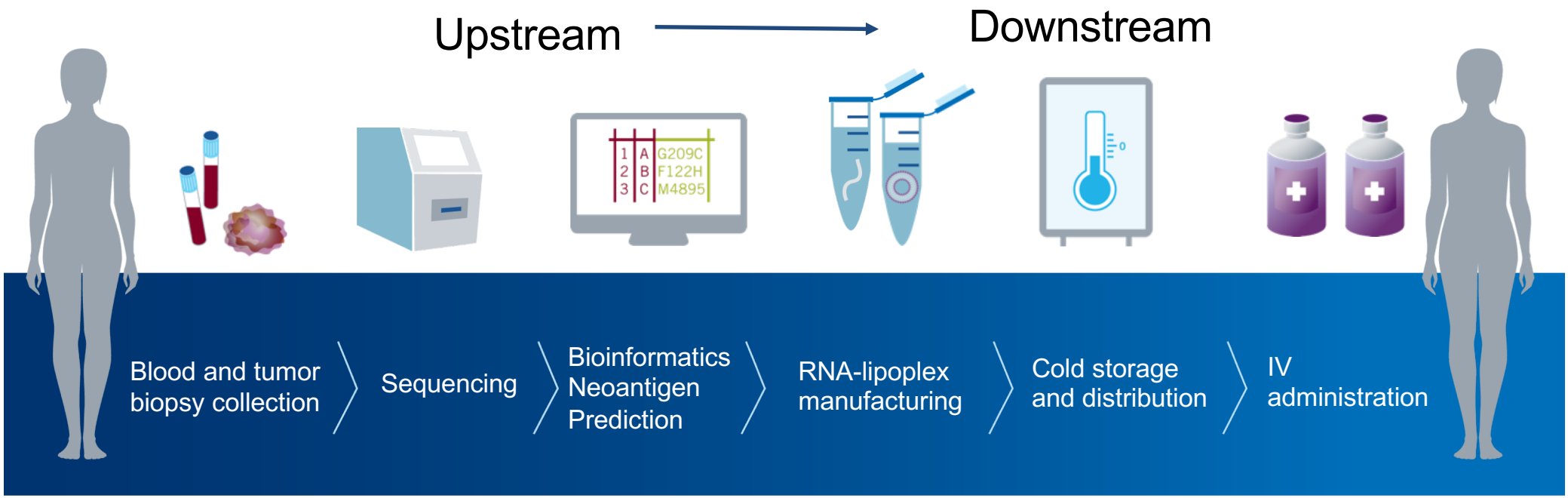
Approach to assessing comparability: As per ICH Q5E

- Different levels, what to compare:
  - Active substance (i.e. mRNAs) and drug products (i.e. lipoplexes)
  - Pair-wise comparison of mRNA and lipoplex batches derived from DNA templates 1, 2, …, and n
  - Comparison of pairs of mRNA and lipoplex batches from existing and new facility
- Parameters to compare:
  - Release testing of active substance and drug product (e.g. RNA content, RNA integrity, nanoparticle size, potency) – within specifications and statistically determined ranges
  - Extended characterization (e.g. residuals not tested for every batch)
  - Stability (with initial read-out based on accelerated and stressed conditions)

iNeST: How to assess updates in neoepitope selection process



Neoepitope selection process: NGS analysis of tumor and blood + bioinformatics analysis of data to identify and prioritize candidate neoantigens for design of each product batch

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Novel regulatory framework for neoantigen-specific immunotherapeutics

- The neoepitope selection process is initiated after a treatment decision has been made, thus “intended use” is design of product for each patient
  - It is *not* used to make treatment decisions or to identify patients or monitor response to treatment
- As such, the neoepitope/target selection process is *not* a diagnostic or companion diagnostic
  - As agreed with US FDA/CBER, EMA, and Health Canada
- This model is pragmatic and provides visibility to the end-to-end production process for individuals who are responsible for evaluating safety and efficacy

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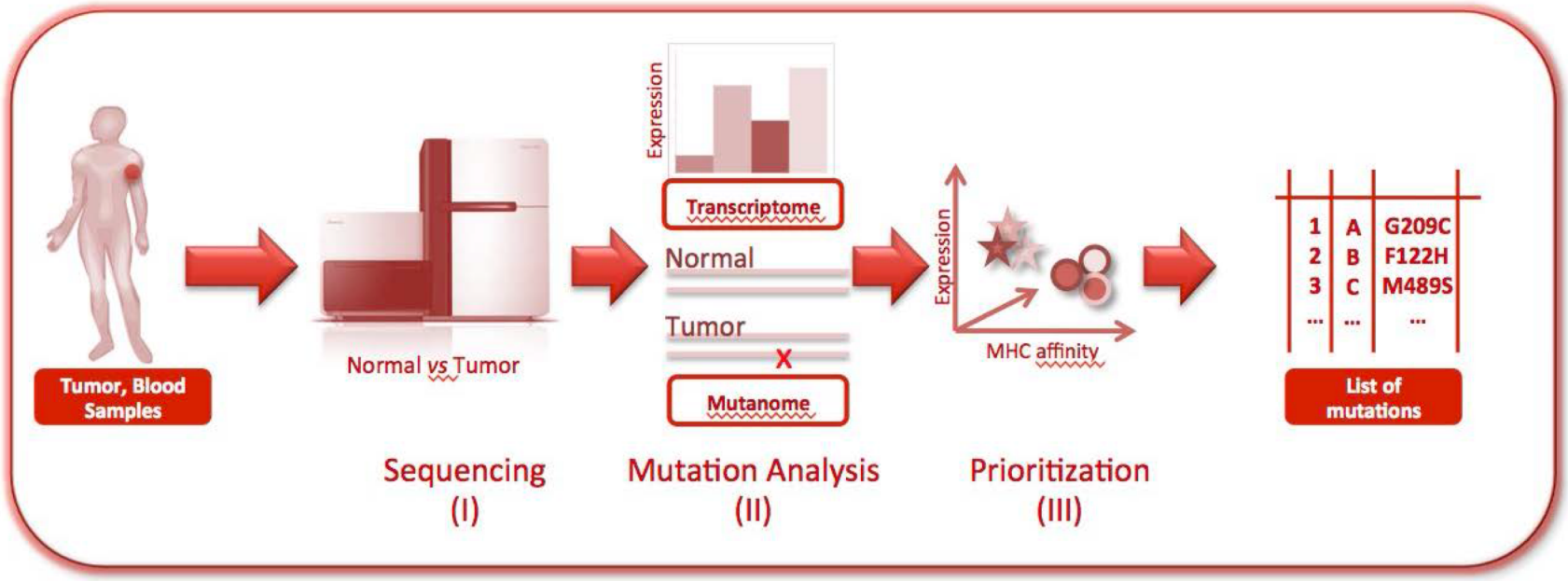
Next-generation sequencing (NGS) data from tumor and blood permits identification of expressed protein-altering somatic mutations



-Exome (tumor and normal) and transcriptome (tumor) sequence alignment

-Somatic mutation calling

-Filtering for expressed protein-altering mutations

-*In silico* translation to obtain mutated peptide candidates

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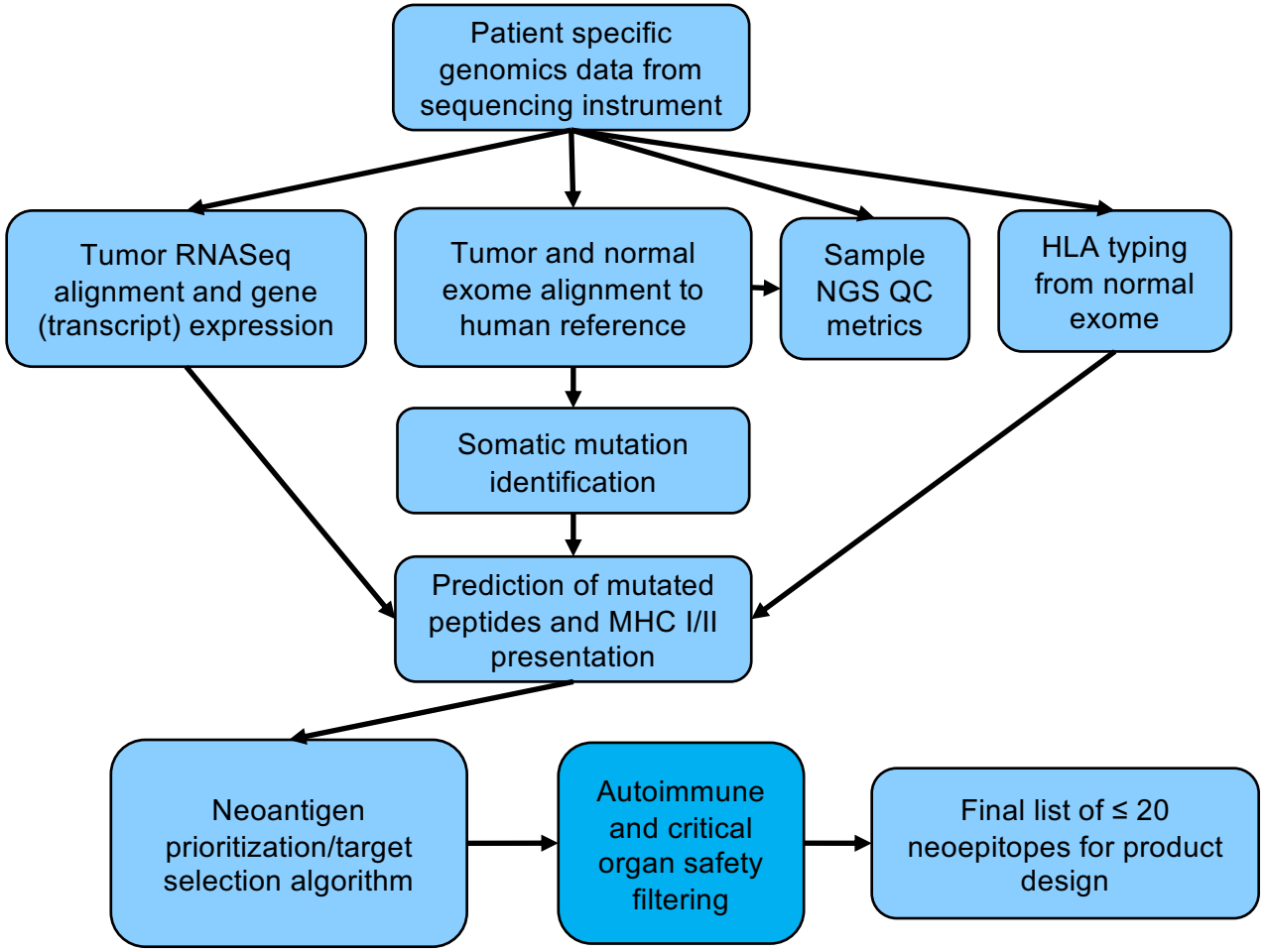
Bioinformatics overview of target selection algorithms



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Summary of candidate neoantigen selection process

Immunogenic neoantigens typically arise from patient-specific passenger mutation/HLA allele combinations, necessitating bioinformatics prioritization.

- Example criteria for neoantigen target prioritization may include
  - Predicted MHC-I and MHC-II binding or presentation
  - Mutation clonality
  - Mutant transcript expression in the tumor
  - Patient safety considerations
- Taking full advantage of rapidly accumulating data may involve…
  - Algorithms that can incorporate all available information and that are matched to data abundance
  - Incorporation of improvements across the workflow, from mutation detection to immune cell stimulation and anti-tumor response
- A regulatory and clinical development framework that enables scientific and technical advances while simultaneously ensuring drug product quality and patient safety

Pre-specified, unit-wise changes: a “do-and-tell” approach enabling timely improvements while providing transparency to regulators

Planning

- Define unit operations.
- Define performance metrics and accept-ability ranges for each.
- Assess requirements for potential improve-ments.
- Assess potential system and patient risks.

Development

- Identify new software components or existing component improvements.
- Select per-unit methods appropriate for extent and nature of available training data.
- Implement.

Assessment & documentation

- Validate new or improved components.
- Demonstrate that all units maintain performance integrity.
- Generate technical report documenting updated performance.
- Track changes through quality management system.

Deploy to production

A pre-specification approach for NGS-based diagnostic tests proposed in FoCR white paper “Charting the Course for Precision Medicine”

Updates in genome sequencing and bioinformatics should be based on *performance metrics*, rather than product comparability

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Conclusions

- Individualized therapeutics are made to order for each patient (e.g. iNeST)
- Flexibility is needed to address the challenges of developing advanced therapies, including those that are individualized.
- This flexibility should *not* result in leniency, but rather adoption of meaningful and appropriate approaches and controls
- Because each batch of an individualized product has unique properties, the standard approach to demonstrating comparability is not possible.

For iNeST products, updates in the neoepitope selection process require conceptually different approaches for demonstrating comparability.

- It is not meaningful to try to make comparisons at the product level.
- Instead, manufacturing updates need to be evaluated at the process level (e.g. performance metrics for defined unit operations)

iNeST

Doing now what patients need next

Roche

iNeST