Individualized Neoantigen Therapy (INT)
The needle-to-needle process

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Cancer Drug Development Forum
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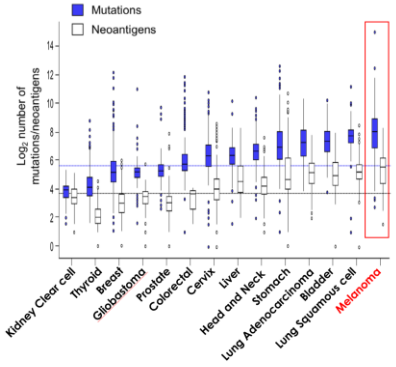
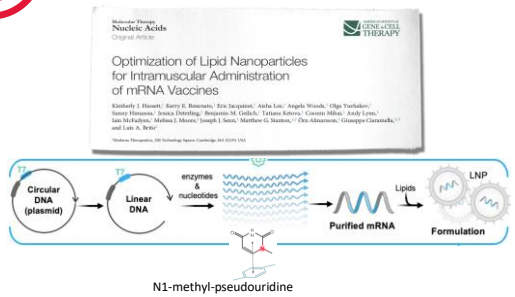
INT developmental history builds on decades of scientific advancements

1970s-Current
Tumor associated antigen modalities fail to demonstrate meaningful clinical improvement; increased focus on neoantigens



1960-Current
mRNA and LNP advancements



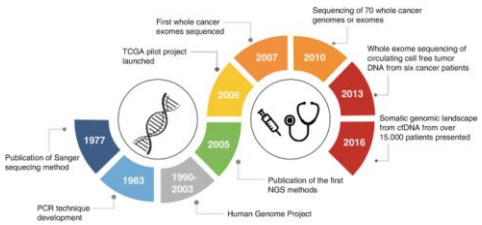
N1-methyl-pseudouridine

Jun 2017
Phase I mRNA-4157-P101 to study mRNA-4157 in patients with resected solid tumors and in combination with pembrolizumab in patients with resected and unresectable solid tumors

2020 - 2021
COVID-19 pandemic impacts clinical trials and provides PoC for mRNA-based modalities

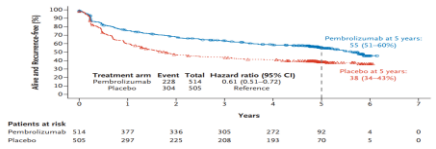
March 2023
PRIME Designation for V940 in melanoma granted

2015 2016 2017 2018 2019 2020 2021 2022 2023 2024



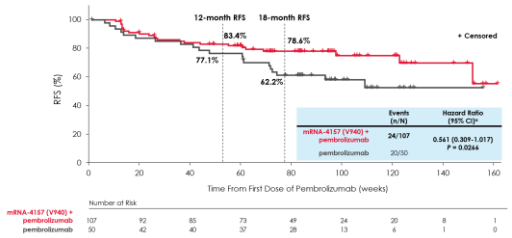
1977-Current
NGS advancements and development of BIX algorithm; Validation of in silico prediction vs ex vivo results

Feb 2019
Randomized Phase 2 mRNA-4157-P201 adjuvant therapy of mRNA-4157 and pembrolizumab versus pembrolizumab alone after complete resection of high-risk melanoma



Feb 2019
Pembrolizumab approved for the treatment of adjuvant melanoma

Nov 2022
Primary analysis of mRNA-4157-P201 met pre-specified statistical significance and showed clinically meaningful RFS and DMFS improvement compared to pembrolizumab



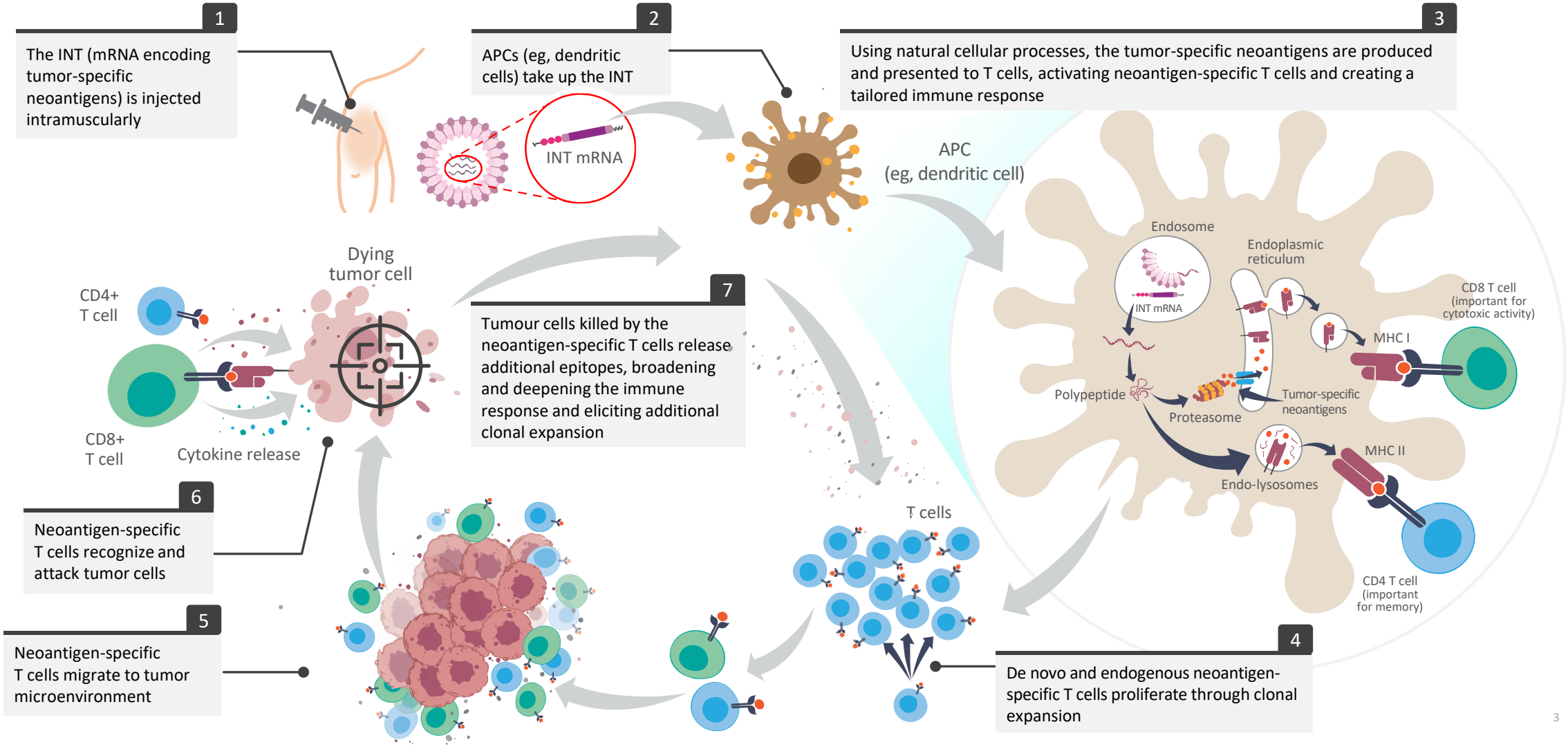
Oct 2023
Phase 3 Randomized, Double-blind, placebo- controlled INTerpath-001 in participants with High-risk Stage II-IV Melanoma

2024
Study continues in INTerpath-001 with 100% of 1089 patients randomized

Karikó K, et al. *Immunity.* 2005 Aug;23(2):165-75. Karikó K, et al. *Mol Ther.* 2008 Nov;16(11):1833-40. Andries O, et al. *J Control Release.* 2015 Nov 10;217:337-44. Tanji H, et al. *Nat Struc Mol Biol.* 2015;22(2):109-15 Edwards DK & Carfi A. *Curr Opin Immunol.* 2022;77:102214.
Hassett KJ, et al. *Mol Ther Nucleic Acids.* 2019;15:1-11. Marganti, S. Role of next-generation sequencing technologies in personalized medicine. P5 eHealth: An Agenda for the Health Technologies of the Future Nature Cancer | VOL 3 | August 2022 | 911–926 R Cristescu et al. Science Oct 2018.

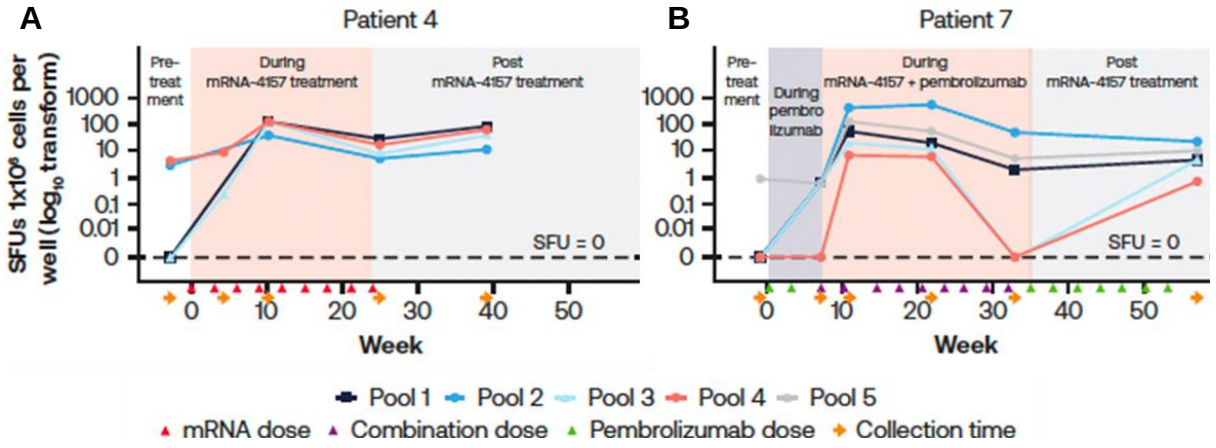
INT mechanism of action

INT trains the immune system's T cells to recognize and attack the patient's unique tumor cells

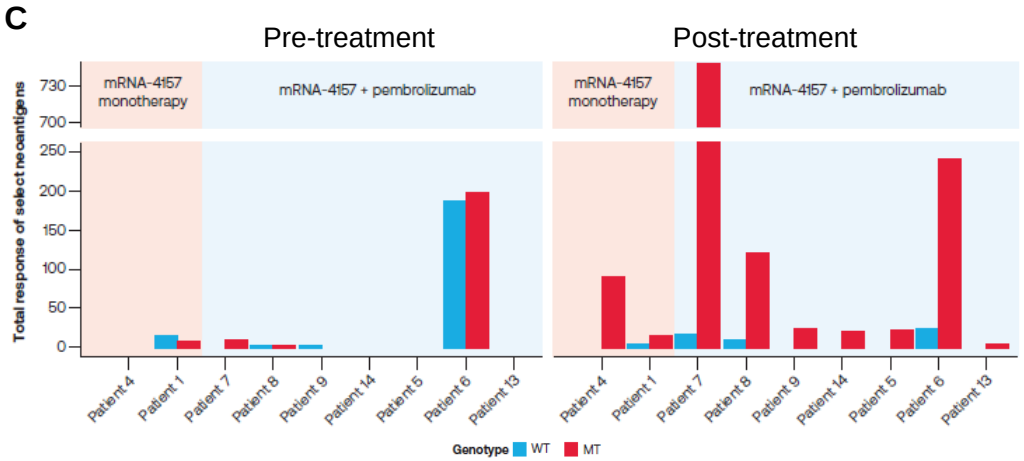


T cell immunogenicity assessment confirms mechanisms of action of V940/INT* (KN-603/P101)

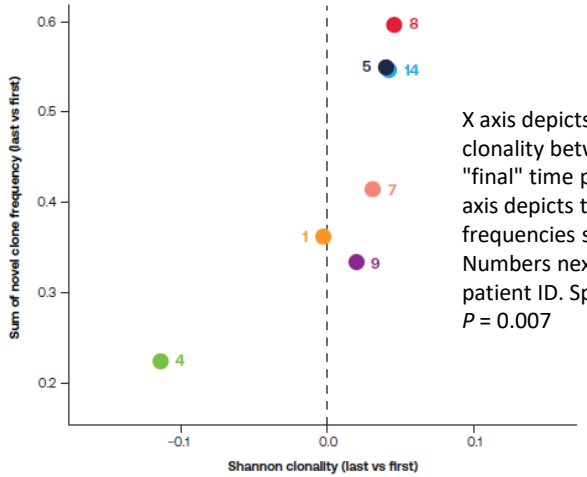
Durability of immune response



Specificity of immune response



Expansion of novel T cell clones



X axis depicts the change in Shannon clonality between the "start" and the "final" time point for each subject. Y axis depicts the sum of novel clone frequencies seen after INT treatment. Numbers next to data spots indicate patient ID. Spearman correlation = 0.93, *P* = 0.007

- Immunogenicity observed as early as 2 cycles post mRNA-4157
- Immunogenicity observed >100 days post last dose of mRNA-4157
- Immunogenicity of INT is specific to the mutant neoantigen
- Expansion of Novel T cell clones observed post INT plus pembrolizumab treatment in adjuvant melanoma (P101, Part D)

*Gainor et al. *Cancer Discovery* (2024).

mRNA Engineering/Formulation[1,2]

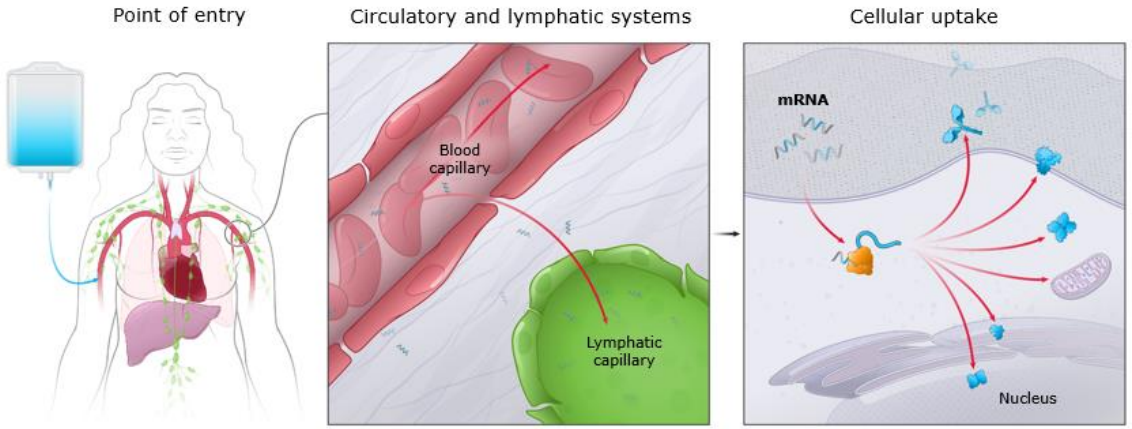
1. Making an mRNA medicine
To protect the mRNA and help deliver it into cells, the mRNA is **wrapped** with lipids, or fats.

2. Deliver mRNA into the body
Individualized neoantigen therapy is given as an injection.

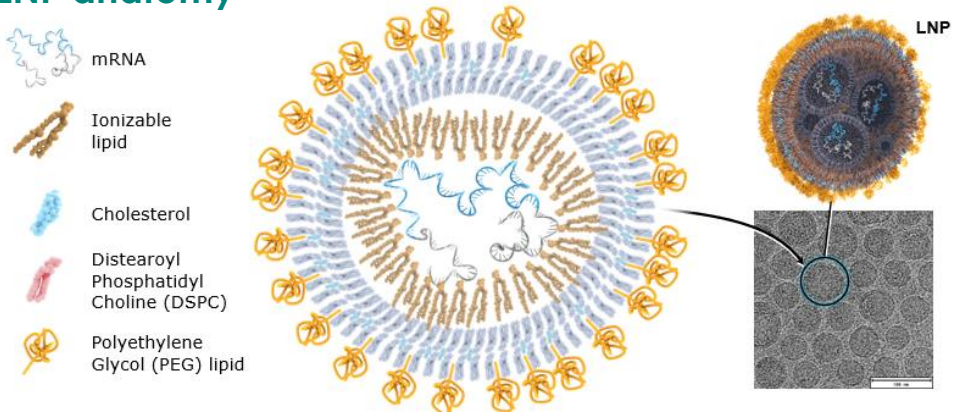
3. Creating the right protein
Once the individualized neoantigen therapy is delivered, the **body takes over** and makes the protein according to the **mRNA's instructions.**

4. Breaking it down
mRNA doesn't stay in the body very long once its job is done, and it does not cause permanent changes or alter DNA.

mRNA medicines must overcome multiple biological barriers



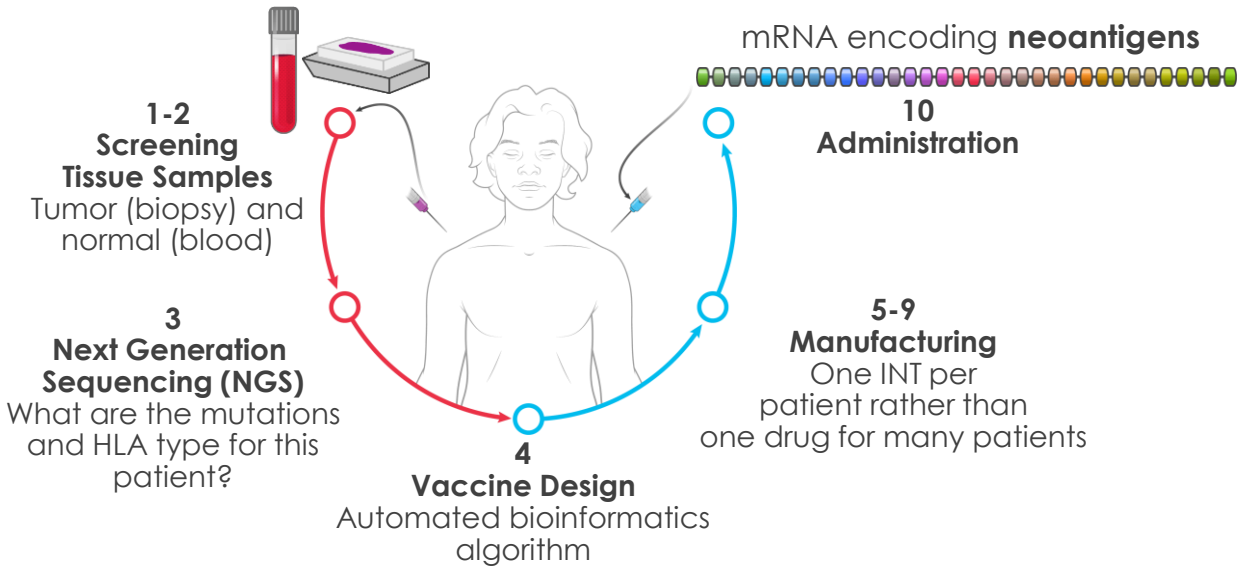
LNP anatomy

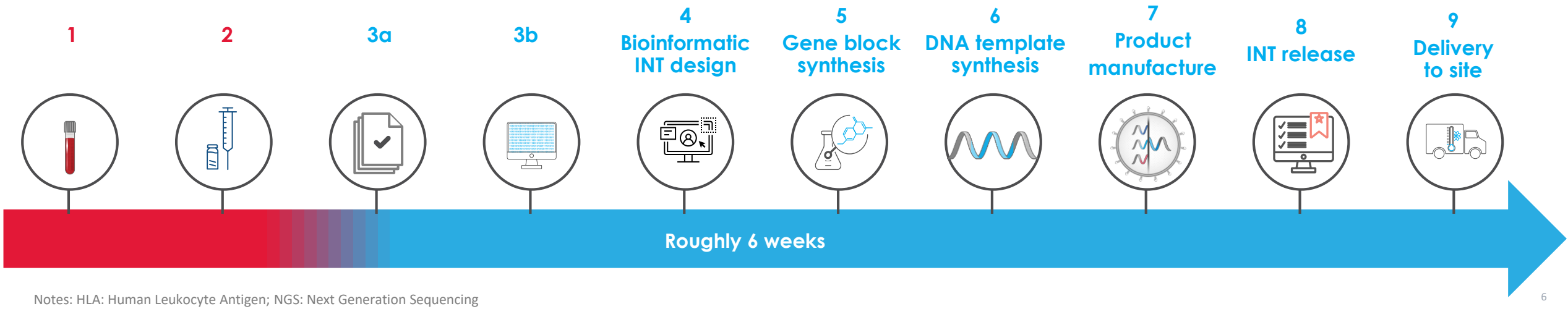


1. Moderna. Power of mRNA. Science of mRNA. Accessed March 9, 2023. https://www.modernatx.com/power-of-mrna/science-of-mrna 2. Edwards DK, Carfi A. *Curr Opin Immunol*. 2022;77:102214.
LNP, lipid nanoparticle

Needle-to-needle process to generate INT

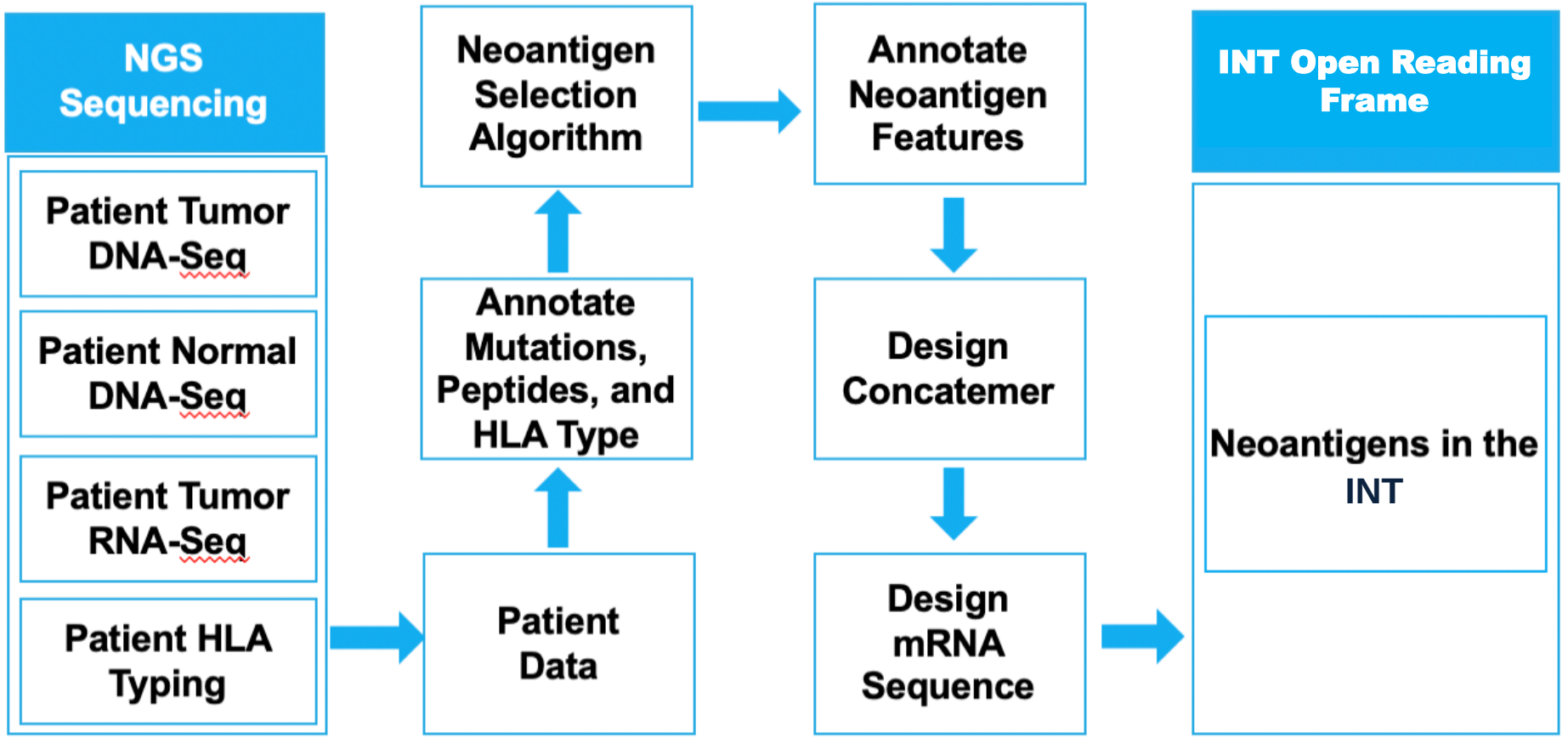
A complex, well defined manufacturing process uses NGS outputs from patient blood and tissue samples to design INT





Notes: HLA: Human Leukocyte Antigen; NGS: Next Generation Sequencing

Algorithm process to design INT



Notes: HLA: Human Leukocyte Antigen; NGS: Next Generation Sequencing

Conclusions

INT has a **novel mode of action**, activating a comprehensive immune response by recognizing cancer neoantigens to mount a tailored anti-tumor effect

INT presents a **new treatment paradigm** as an **individualized product**, with important considerations for needle-to-needle delivery to patients

There are **unique aspects for manufacturing** (NGS and bioinformatics) and important considerations for **product release** (small batch size, and short release timeline)

INT has the potential to treat **different cancer types** and benefit a broad patient population including as a **curative treatment** of early-stage immune-responsive cancers

Thank you