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Cancer vaccines: from concept to reality

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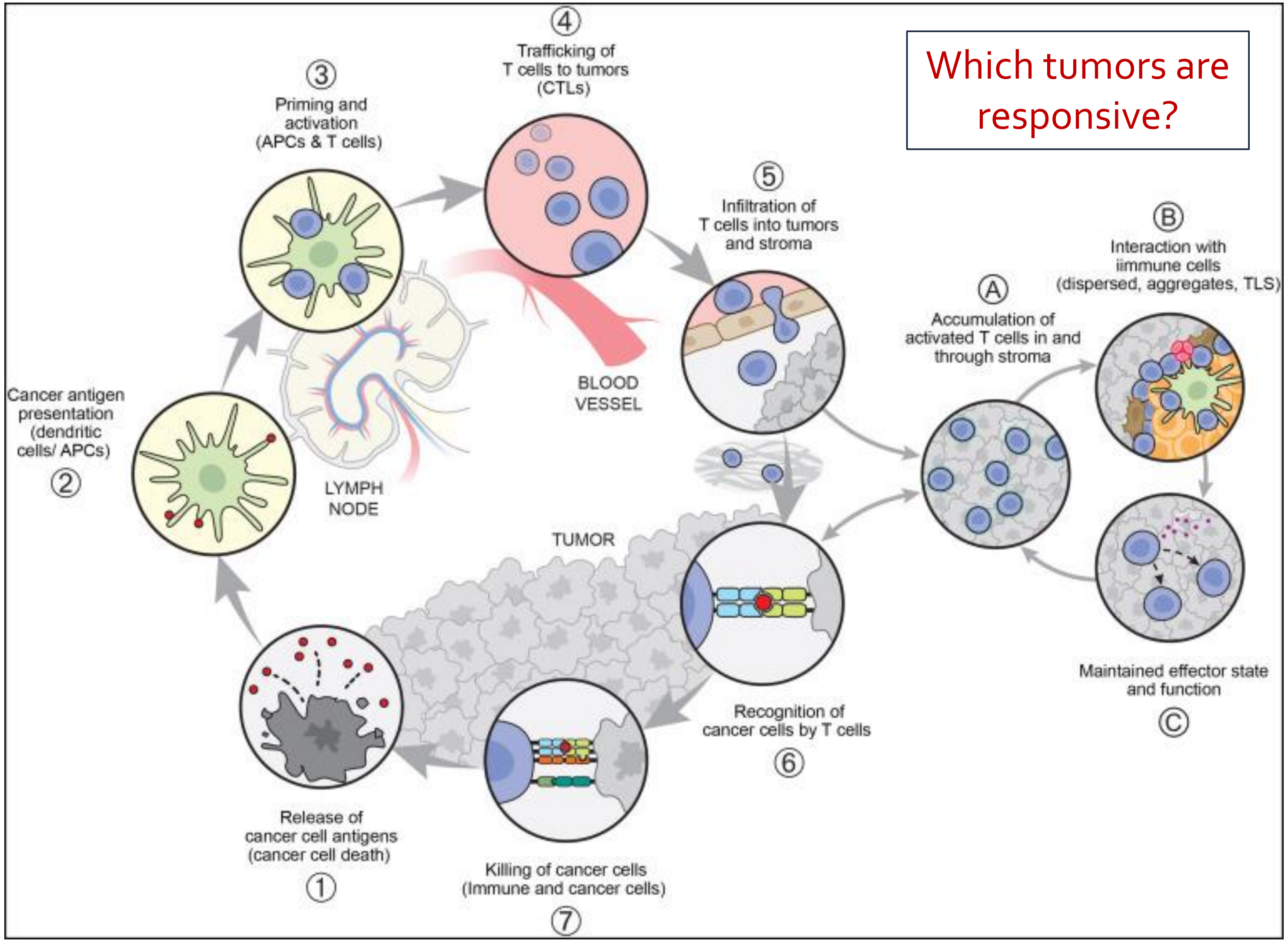
VUB VRIJE UNIVERSITEIT BRUSSEL

At the basis of it all: the cancer-immunity cycle

How to present tumor antigens to T cells?

Which tumor antigens?



Which tumors are responsive?

Mellman et al, Volume 56, Issue 10, p2188-2205October 10, 2023

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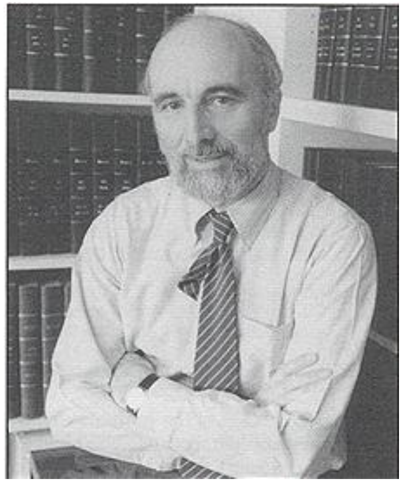
Which tumor antigens?



Thierry Boon

Pierre van der Bruggen

Tumor characterizing antigens

- **1977 - Thierry Boon (Belgium - Ludwig Institute):** 'Boon T, Kellermann O., Rejection by syngeneic mice of cell variants obtained by mutagenesis of a malignant teratocarcinoma cell line, Proc Natl Acad Sci U S A. 1977 Jan;74(1):272-5.'

- **van der Bruggen P**., Traversari C., Chomez P., Lurquin C., De Plaen E., Van den Eynde B., Knuth A., **Boon T**. A gene encoding an antigen recognized by cytolytic T lymphocytes on a human melanoma. Science. 1991 Dec 13;254(5038):1643–1647

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Which tumor antigens?

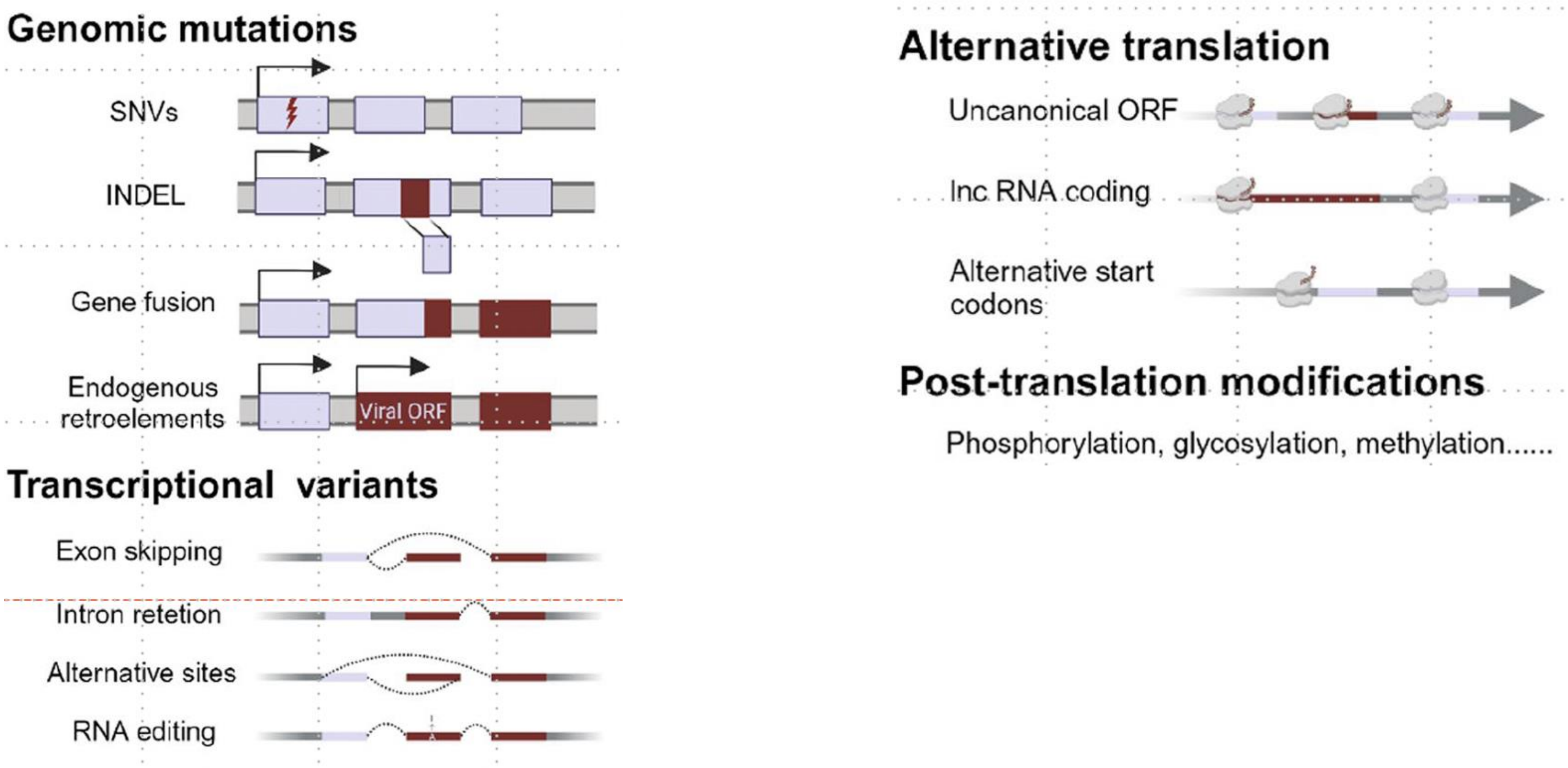
Tumor-associated antigens

- Not unique to tumors
- **Overexpressed proteins** (e.g. survivin, MUC-1/2), **cancer germline proteins** (oncofetal, cancer-testis: e.g. MAGE, GAGE, BAGE, NY-ESO-1), **tissue-differentiation proteins** (e.g. tyrosinase, Melan-A/MART-1, gp100, TRP-1/2)

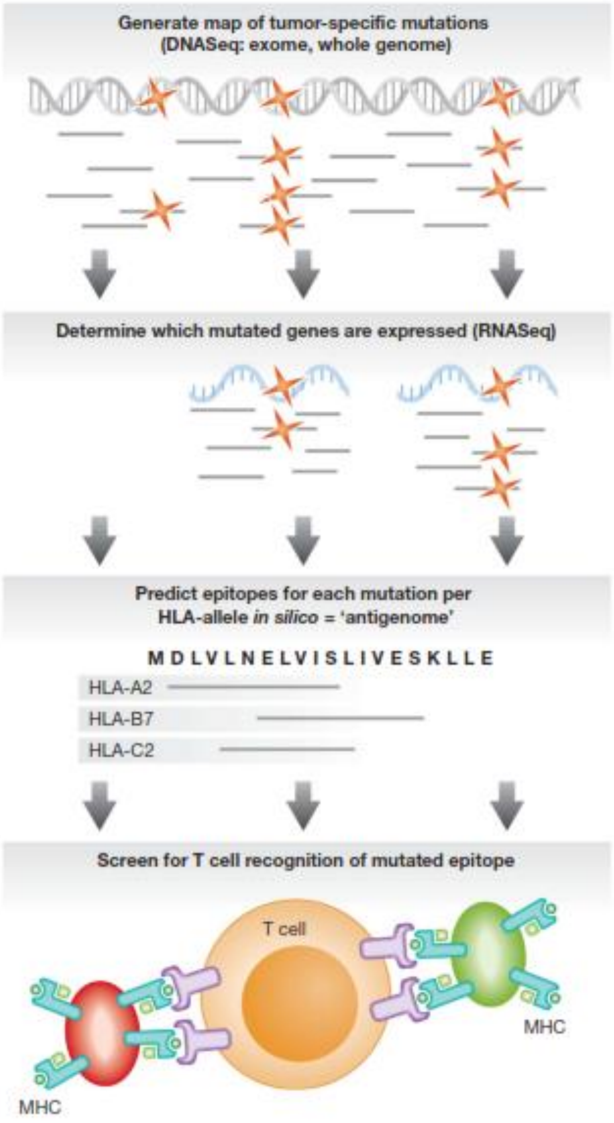
Tumor-specific antigens

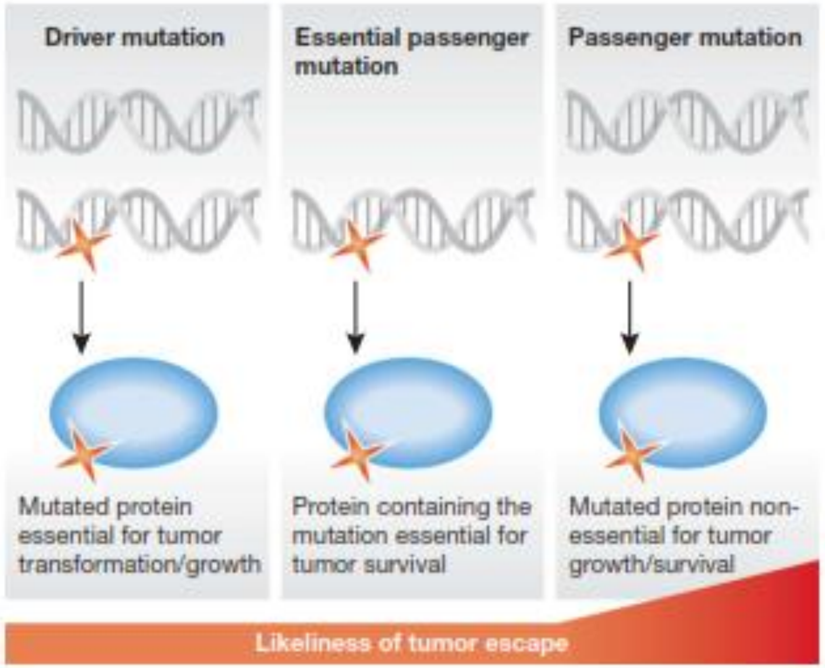
- Unique to tumors
- **Neo-epitopes** (e.g. EGFRvIII, $KRAS^{G12C}$, $BRAF^{V600E}$ vs patient-specific)
- **Viral antigens** (e.g. HPV E6/E7 => responsible for nearly all cervical cancers, but also throat, anus, penis,…)

Which tumor antigens: neo-epitopes



Which tumor antigens: the cancer antigenome





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Which tumor antigens: neo-epitopes derived from the dark genome

COMMENT | 24 January 2013

The dark matter of genome

It has three billion base pairs but only about two per cent of the human genome codes for proteins. In a two part series, Pawan Dhar tries to understand what the remaining bulk of the human genome is doing? Is it a genetic graveyard or a cryptic instruction manual that ensures survival of the species?

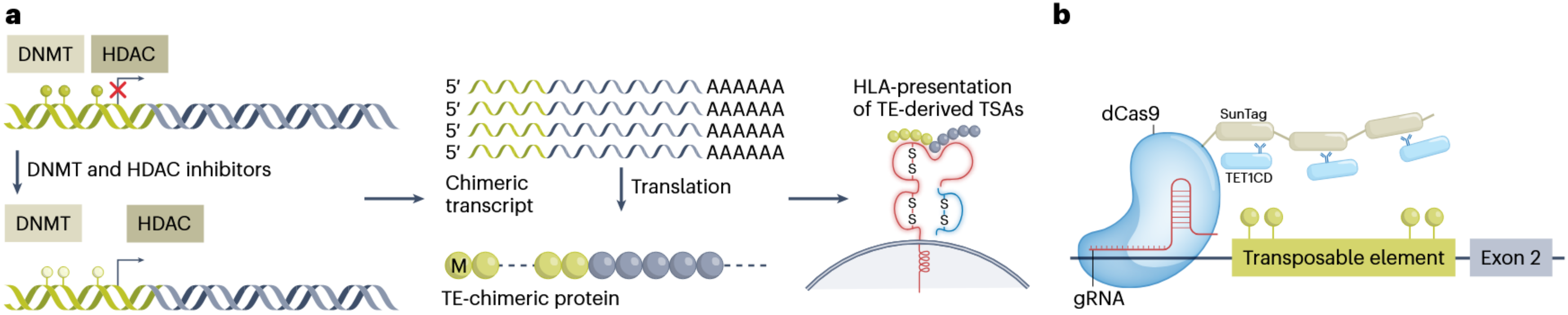
The recent ENCODE (Encyclopedia of DNA Elements) project has thrown new light on the dark matter of genome – traditionally labelled junk. It turns out that more than 80% of the human 'non-protein coding' genome is biologically active and impacts the expression of genes in the neighbourhood.

Which tumor antigens: neo-epitopes derived from the dark genome

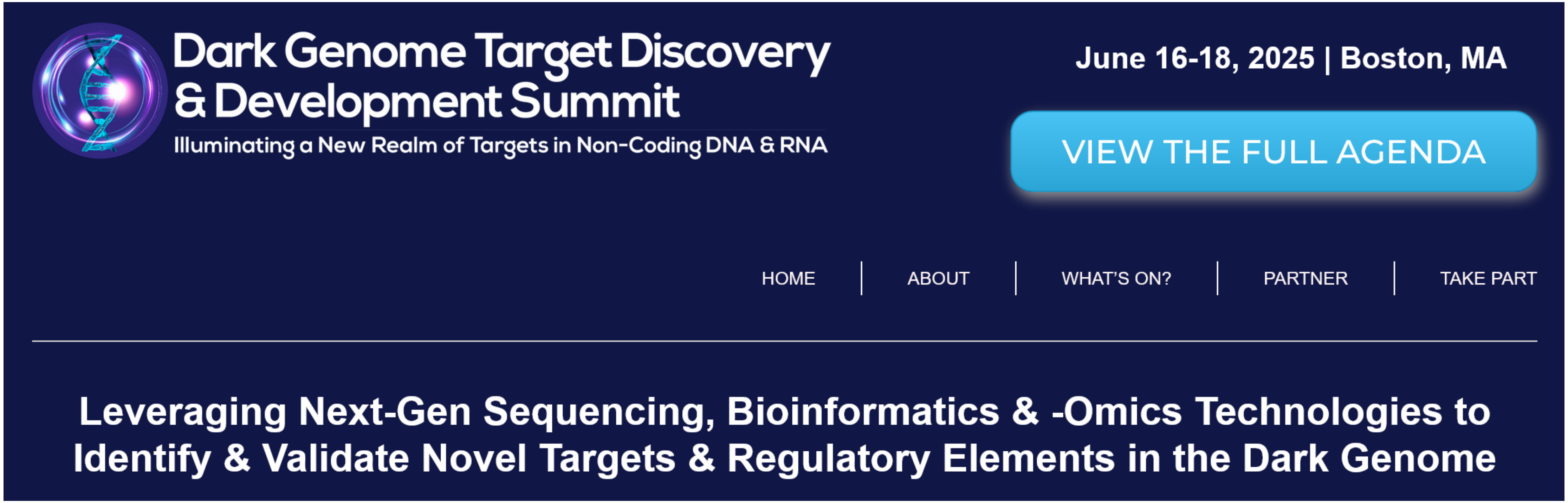
nature genetics Volume 56 | September 2024 | 1770–1771 |

Glioblastoma therapy https://doi.org/10.1038/s41588-024-01850-3

Activating the dark genome to illuminate cancer vaccine targets



Which tumor antigens: neo-epitopes derived from the dark genome



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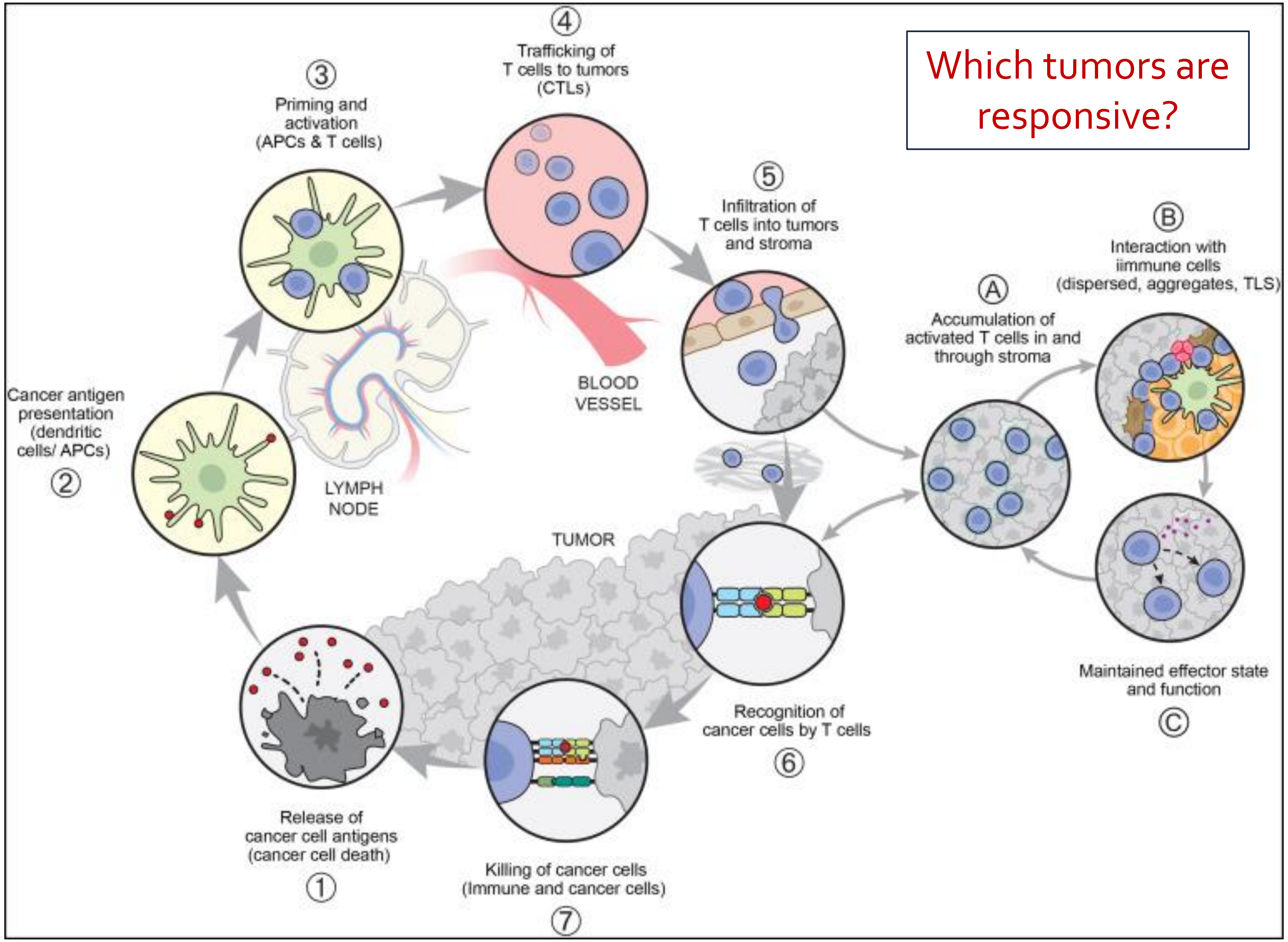

Which tumors are responsive?

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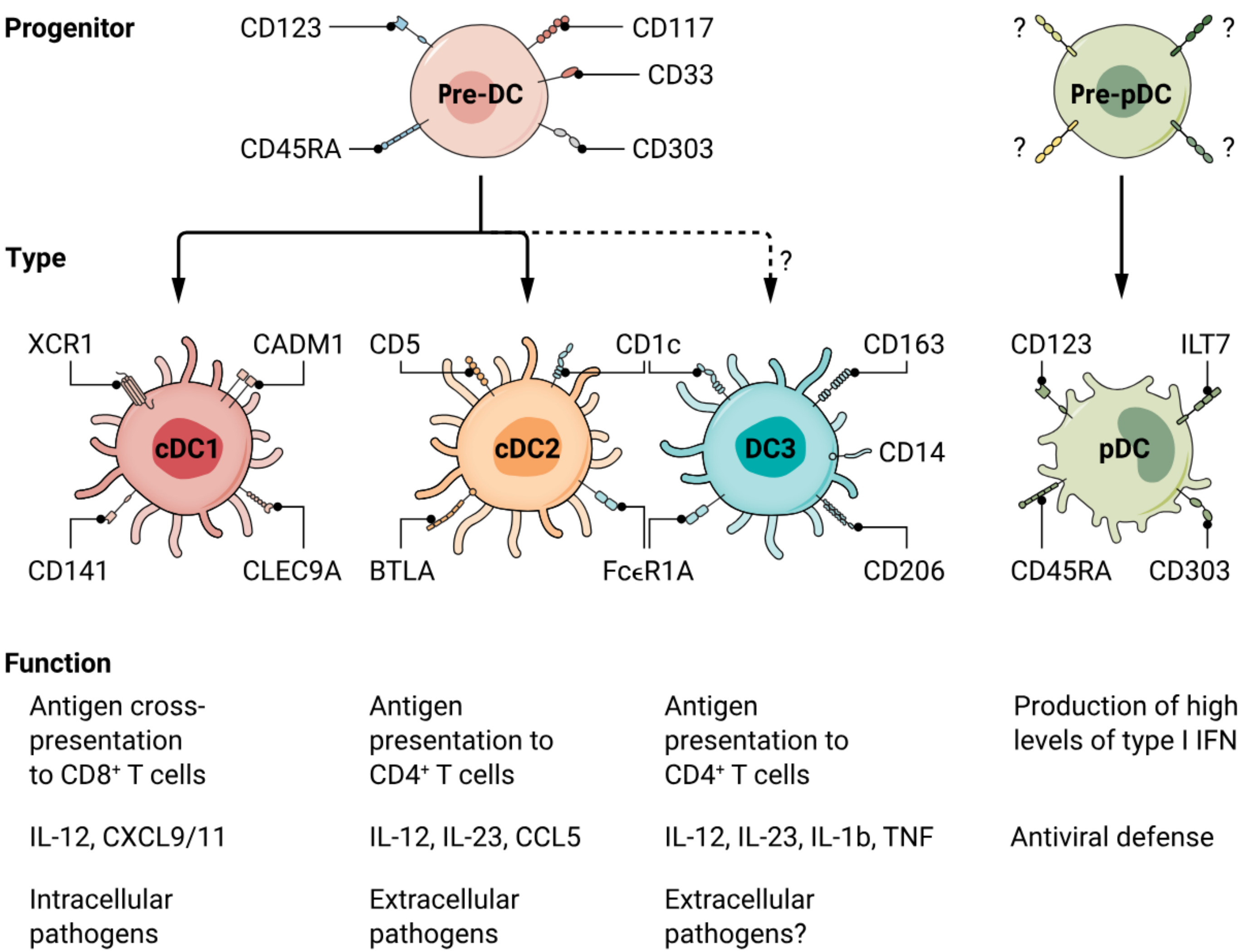
How to present tumor antigen to T cells: current knowledge on human DCs



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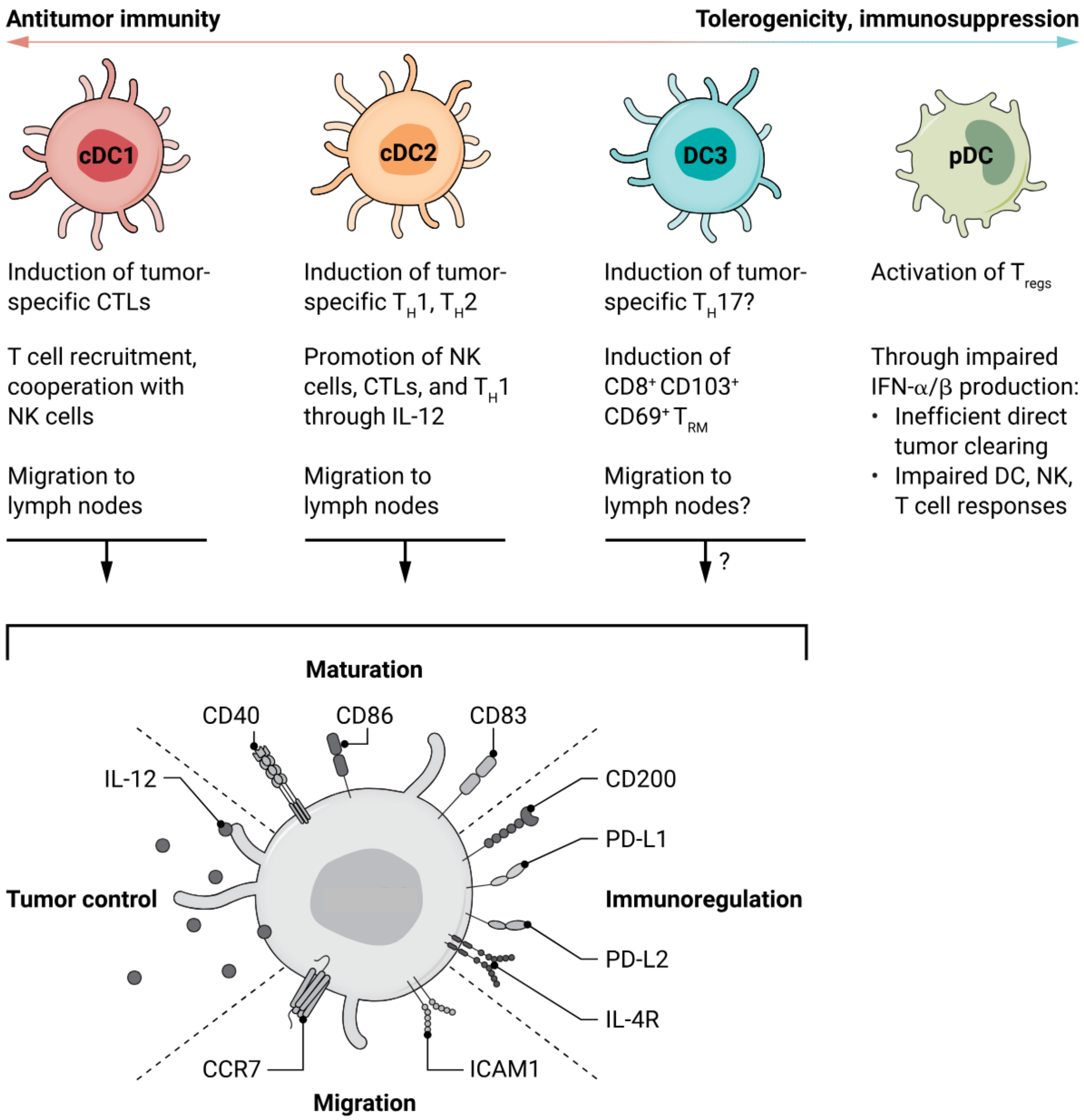
How to present tumor antigen to T cells: human DCs in cancer



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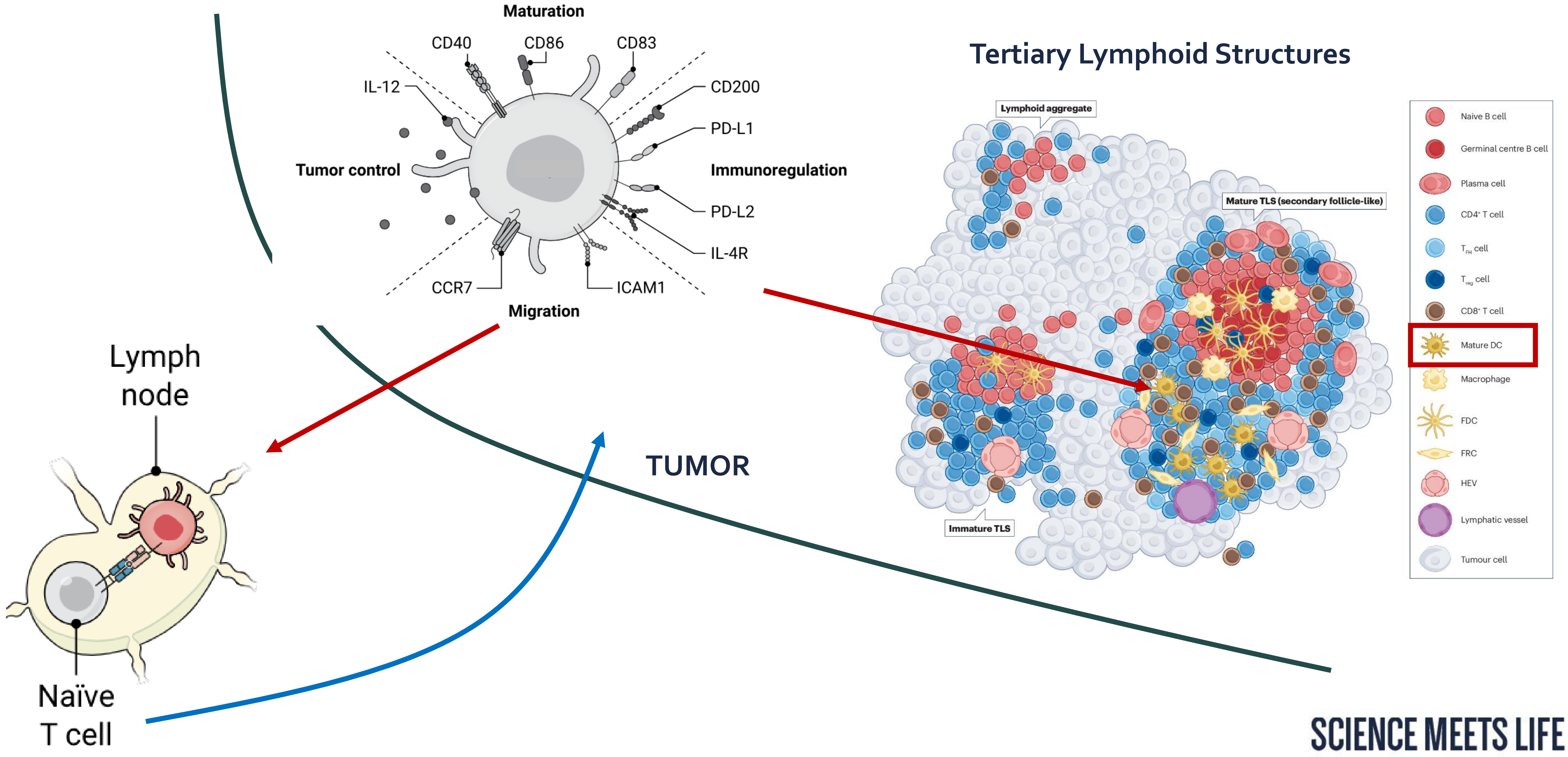
DCs present tumor antigens in tertiary lymphoid organs or lymph nodes



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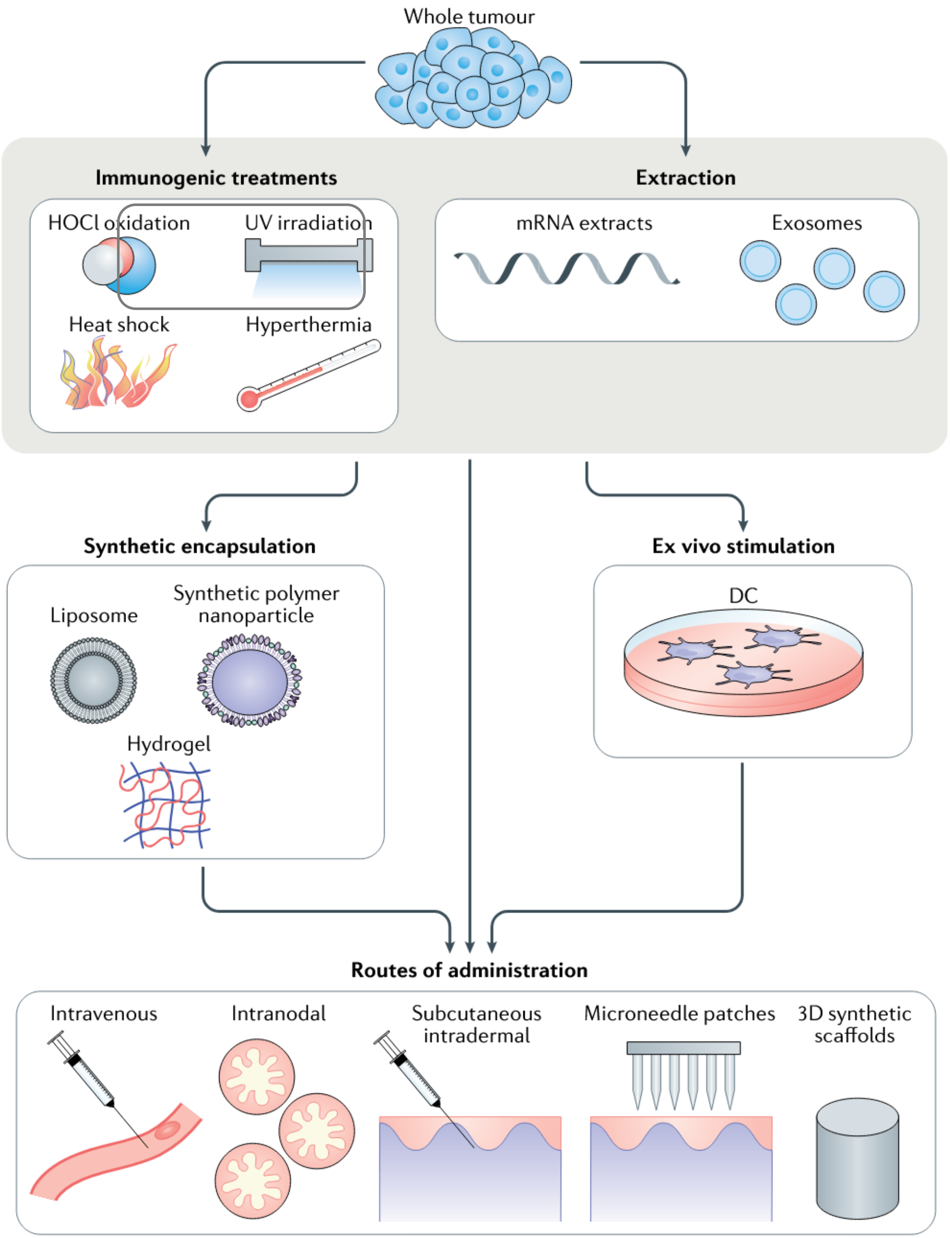
Employment of DCs as cancer vaccines

Immunogenic
cell death
inducers
⇒ Chemo
⇒ Radiation



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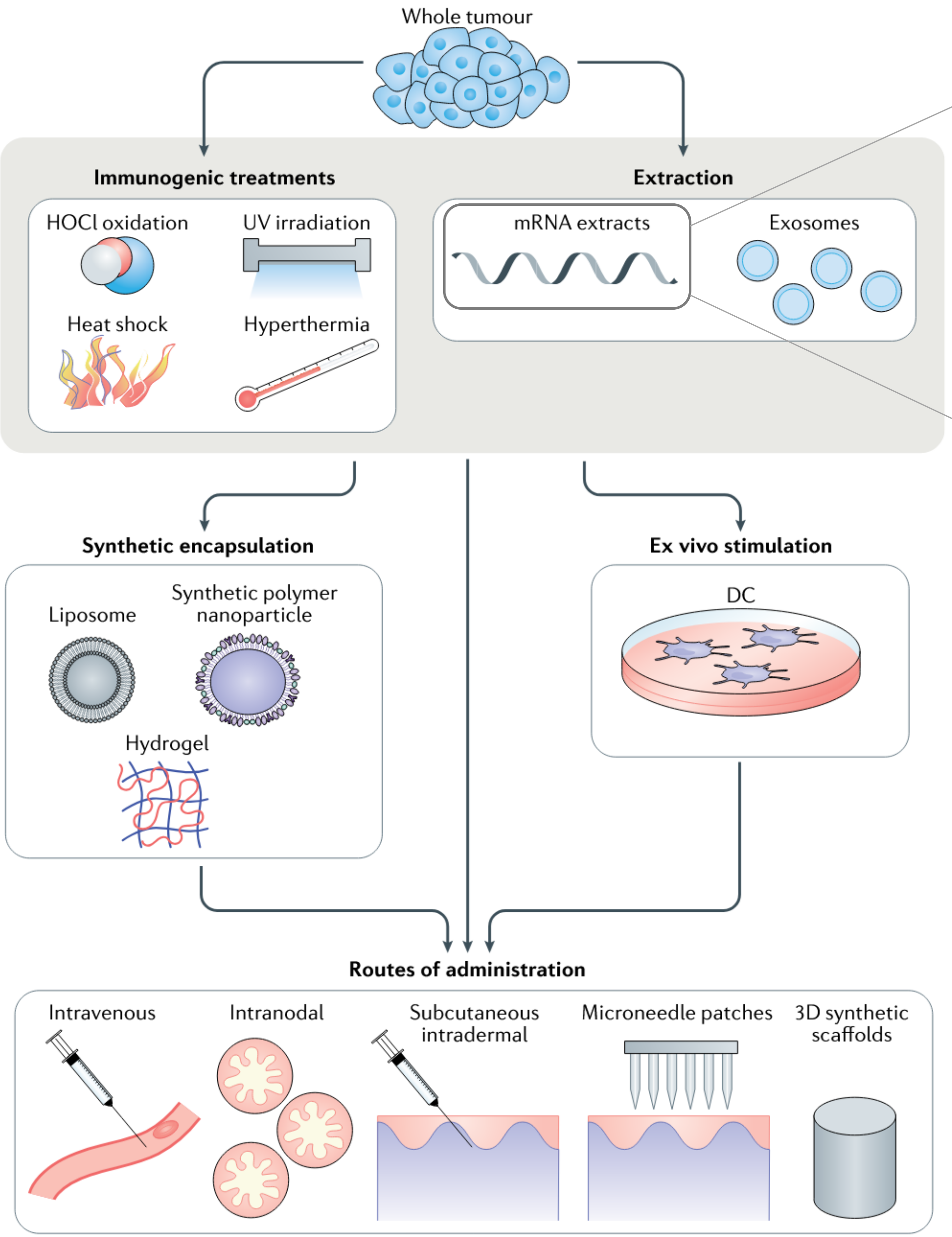

Article

RNA neoantigen vaccines prime long-lived CD8⁺ T cells in pancreatic cancer

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Zachary Sethna[1,2,3,4,14], Pablo Guasp[1,2,14], Charlotte Reiche[1,2], Martina Milighetti[1,2,4], Nicholas Ceglia[4], Erin Patterson[3], Jayon Lihm[3,4], George Payne[1,2], Olga Lyudovyk[4], Luis A. Rojas[1,2], Nan Pang[2], Akihiro Ohmoto[1,2], Masataka Amisaki[1,2], Abderezak Zebboudj[1,2], Zagaa Odgerel[1,2], Emmanuel M. Bruno[1,2], Siqi Linsey Zhang[1,2], Charlotte Cheng[1,2], Yuval Elhanati[4], Evelyna Derhovanessian[5], Luisa Manning[5], Felicitas Müller[5], Ina Rhee[6], Mahesh Yadav[6], Taha Merghoub[7], Jedd D. Wolchok[7], Olca Basturk[8], Mithat Gönen[9], Andrew S. Epstein[10], Parisa Momtaz[10], Wungki Park[10,11], Ryan Sugarman[10], Anna M. Varghese[10], Elizabeth Won[10], Avni Desai[10], Alice C. Wei[2,11], Michael I. D'Angelica[2,11], T. Peter Kingham[2,11], Kevin C. Soares[2,11], William R. Jarnagin[2,11], Jeffrey Drebin[2,11], Eileen M. O'Reilly[10,11], Ira Mellman[6], Ugur Sahin[5,12], Özlem Türeci[5,12], Benjamin D. Greenbaum[3,4,13,15] & Vinod P. Balachandran[1,2,3,11,15] ✉

LETTER

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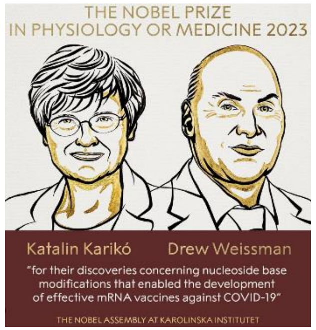
Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer

Ugur Sahin[1,2,3], Evelyna Derhovanessian[1], Matthias Miller[1], Björn-Philipp Kloke[1], Petra Simon[1], Martin Löwer[2], Valesca Bukur[1,2], Arbel D. Tadmor[2], Ulrich Luxemburger[1], Barbara Schrörs[2], Tana Omokoko[1], Mathias Vormehr[1,3], Christian Albrecht[2], Anna Paruzynski[1], Andreas N. Kuhn[1], Janina Buck[1], Sandra Heesch[1], Katharina H. Schreeb[1], Felicitas Müller[1], Inga Ortseifer[1], Isabel Vogler[1], Eva Godehardt[1], Sebastian Attig[2,3], Richard Rae[2], Andrea Breitkreuz[1], Claudia Tolliver[1], Martin Suchan[2], Goran Martic[2], Alexander Hohberger[3], Patrick Sorn[2], Jan Diekmann[1], Janko Ciesla[4], Olga Waksmann[4], Alexandra-Kemmer Brück[1], Meike Witt[1], Martina Zillgen[1], Andree Rothermel[2], Barbara Kasemann[2], David Langer[1], Stefanie Bolte[1], Mustafa Diken[1,2], Sebastian Kreiter[1,2], Romina Nemecek[5], Christoffer Gebhardt[6,7], Stephan Grabbe[3], Christoph Höller[5], Jochen Utikal[6,7], Christoph Huber[1,2,3], Carmen Loquai[3]* & Özlem Türeci[8]*



***Katalin Karikó**, Nobel Laureate, Consultant, BioNTech*
***Prof. Ugur Sahin**, MD, CEO BioNTech*
***Prof. Özlem Türeci**, MD, Chief Medical Officer of BioNTech*

Employment of DCs as cancer vaccines

Immunogenic cell death inducers
⇒ Chemo
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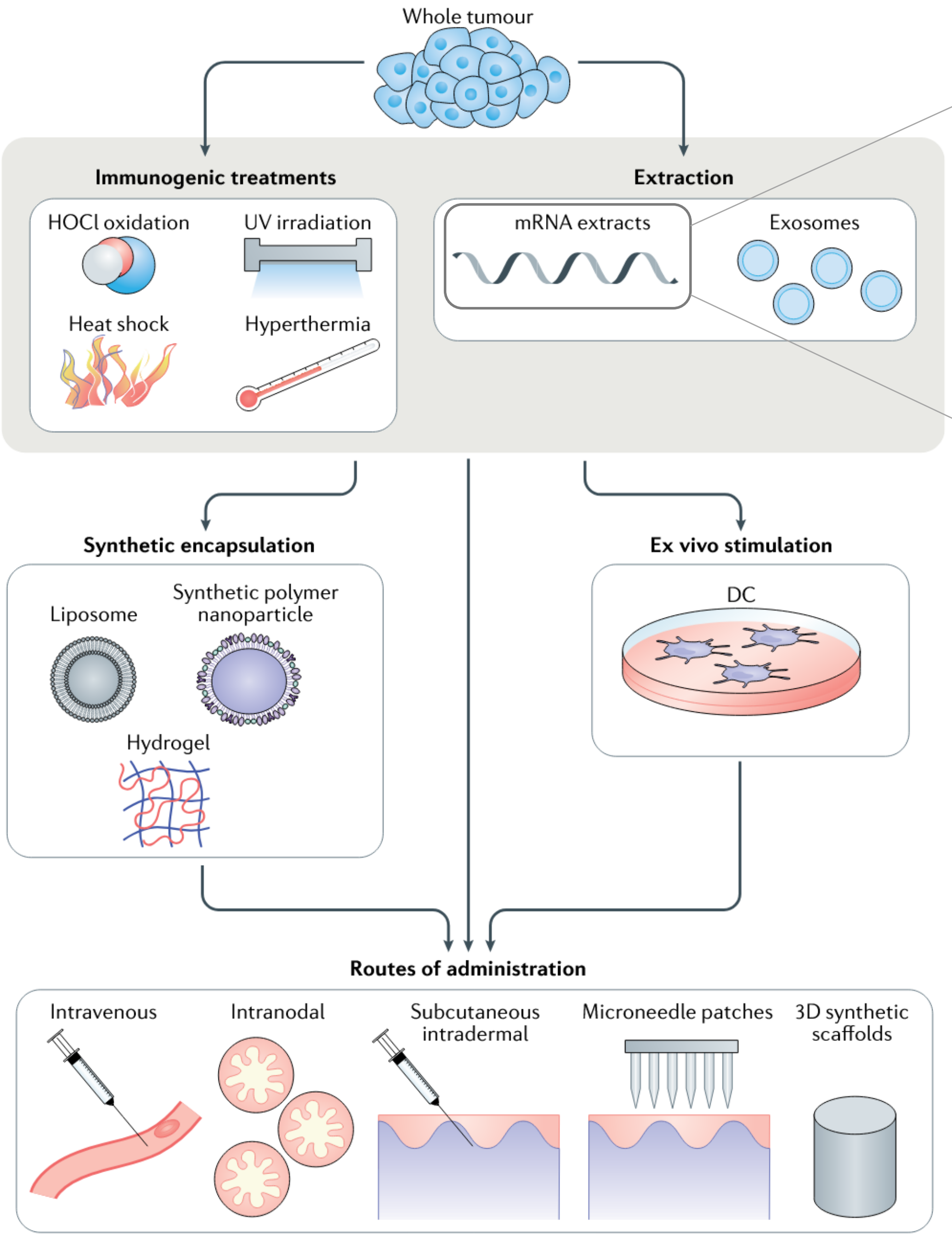

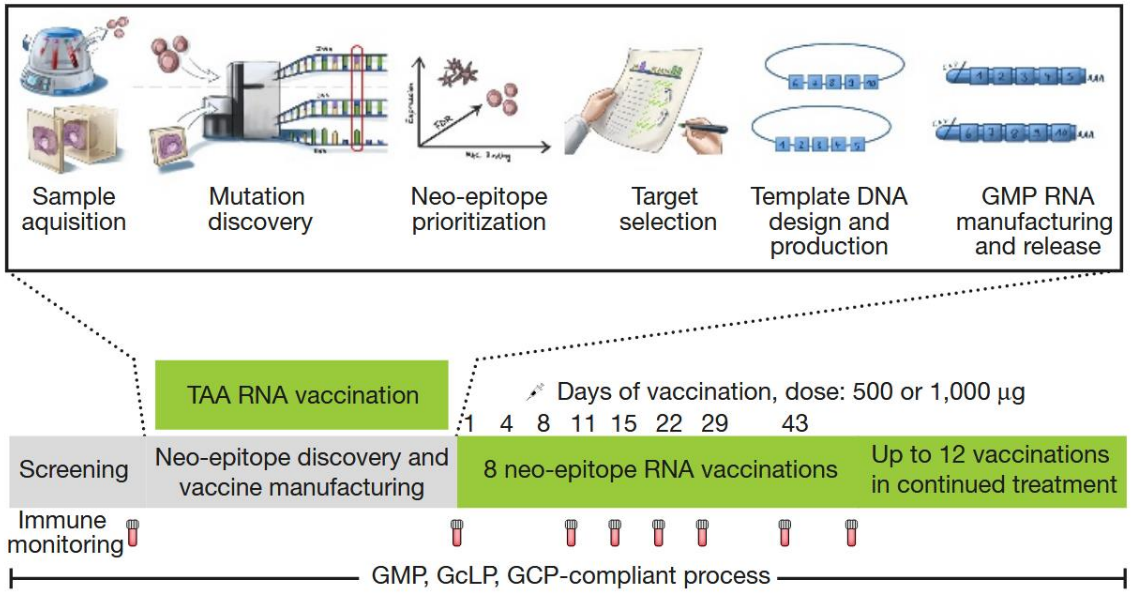

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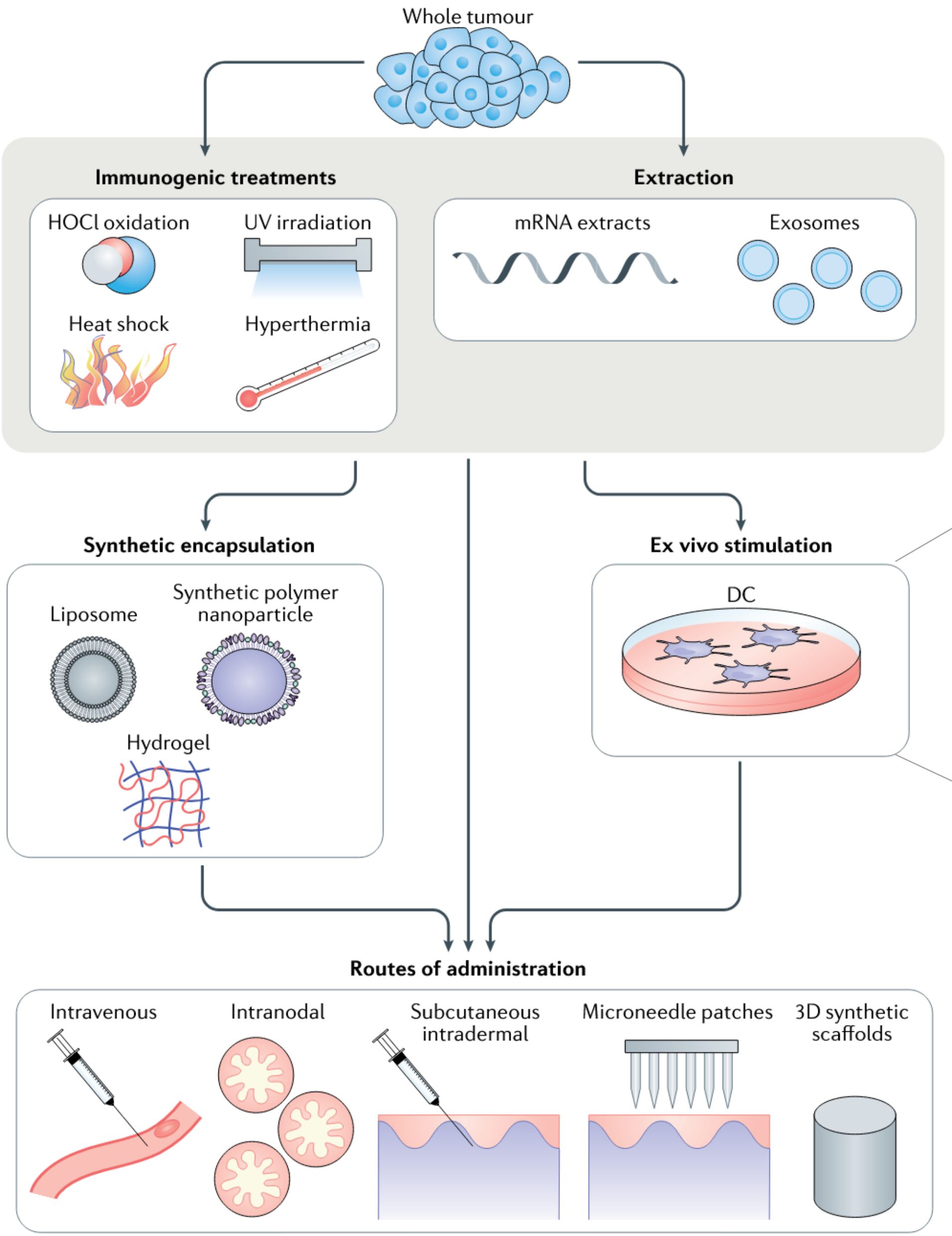
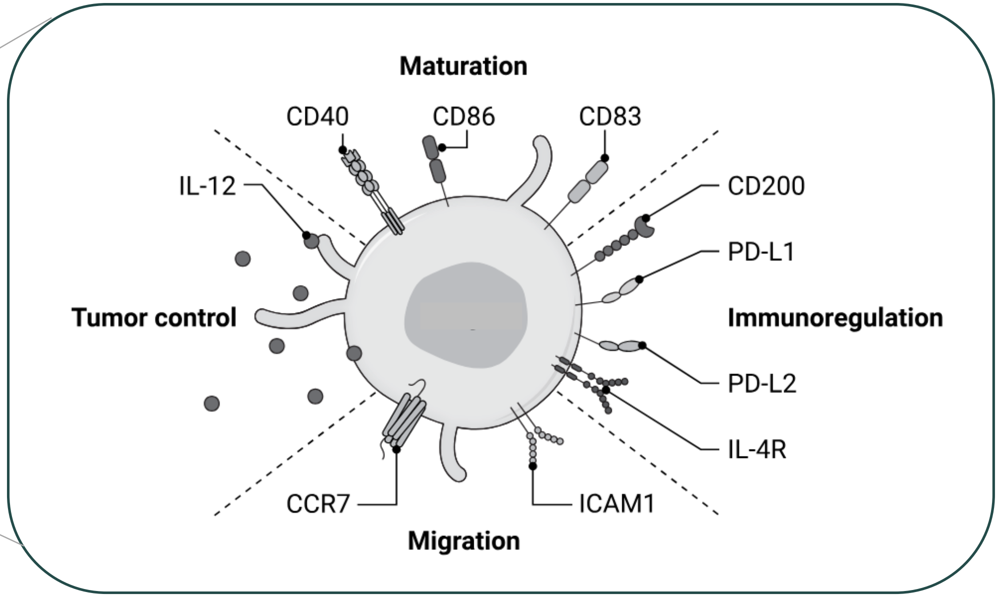


Which DC type?



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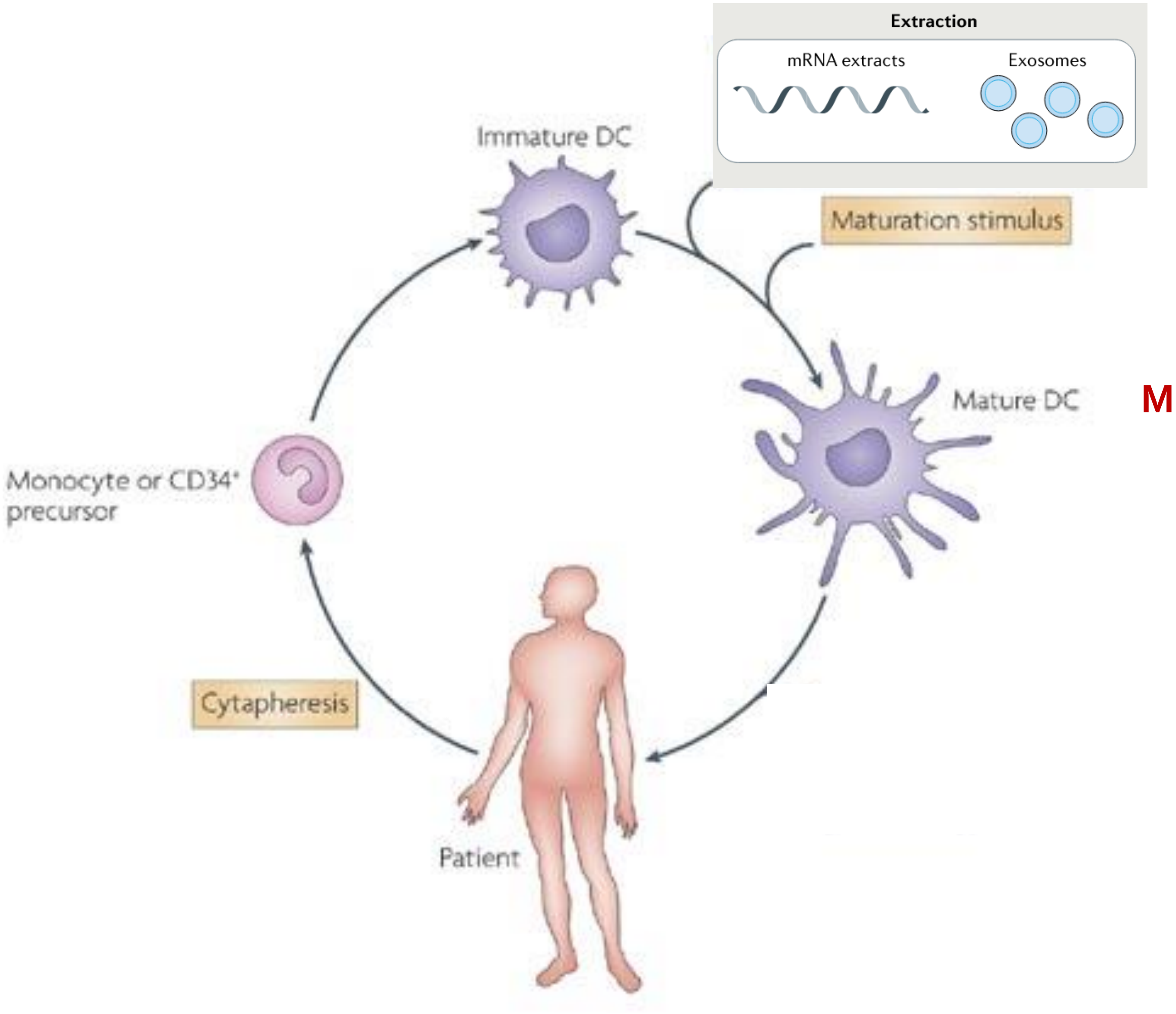
Employment of DCs as cancer vaccines

cDC
Pre-cDC



Mature cDC1/2

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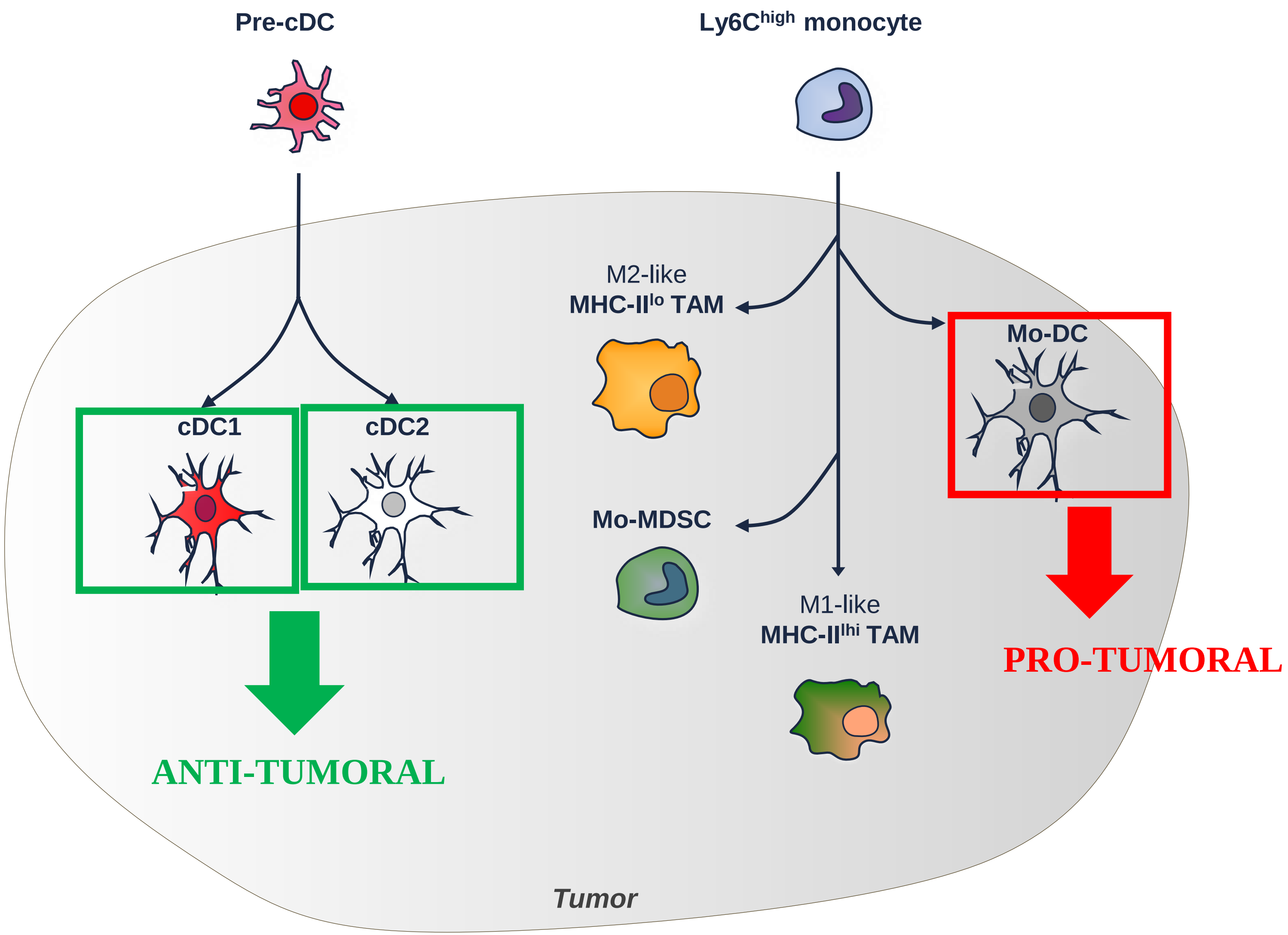
Employment of tumor-infiltrating DCs as cancer vaccines



Damya Laoui

BRUSSELS CENTER FOR IMMUNOLOGY RESEARCH GROUP

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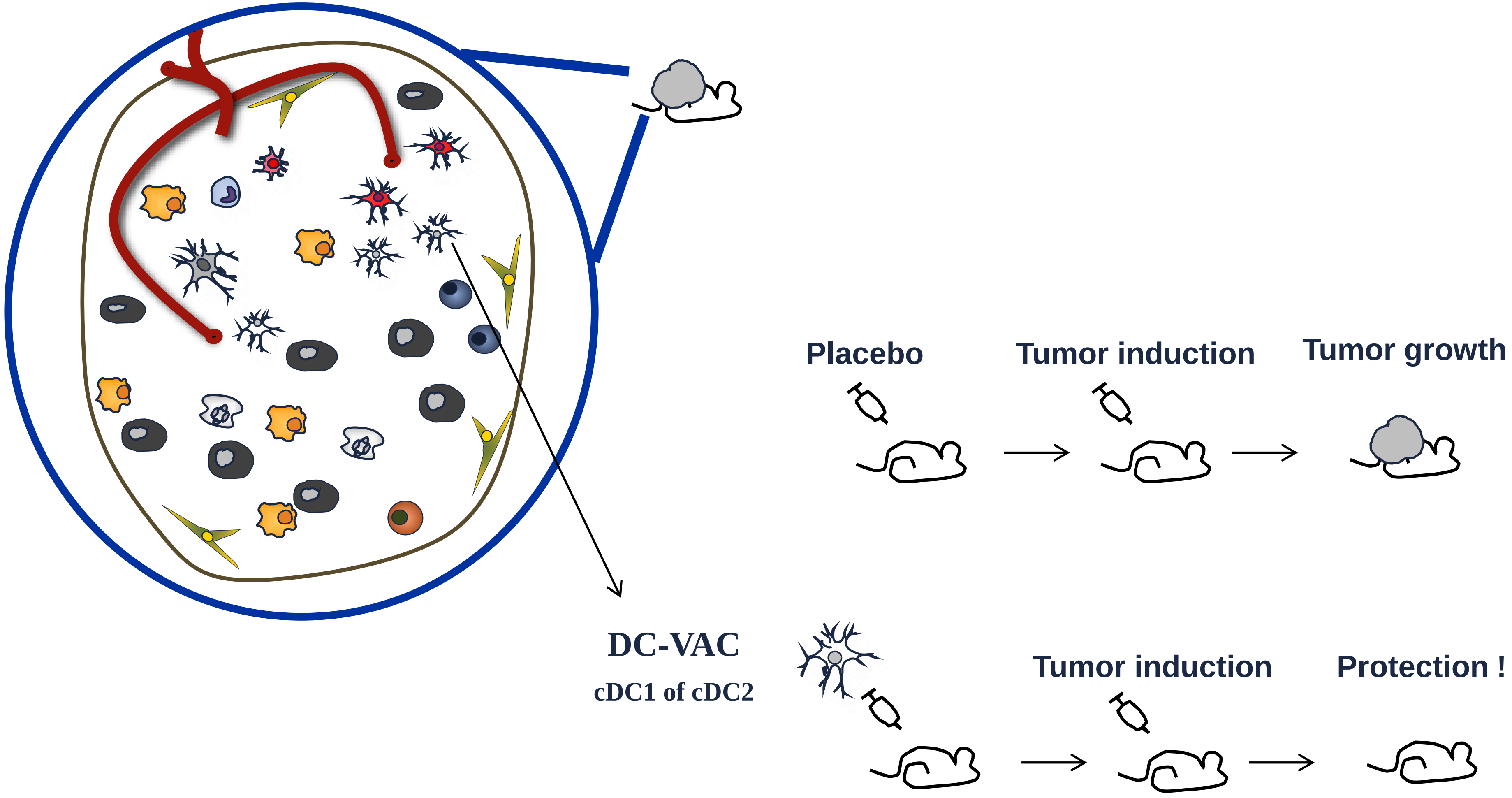

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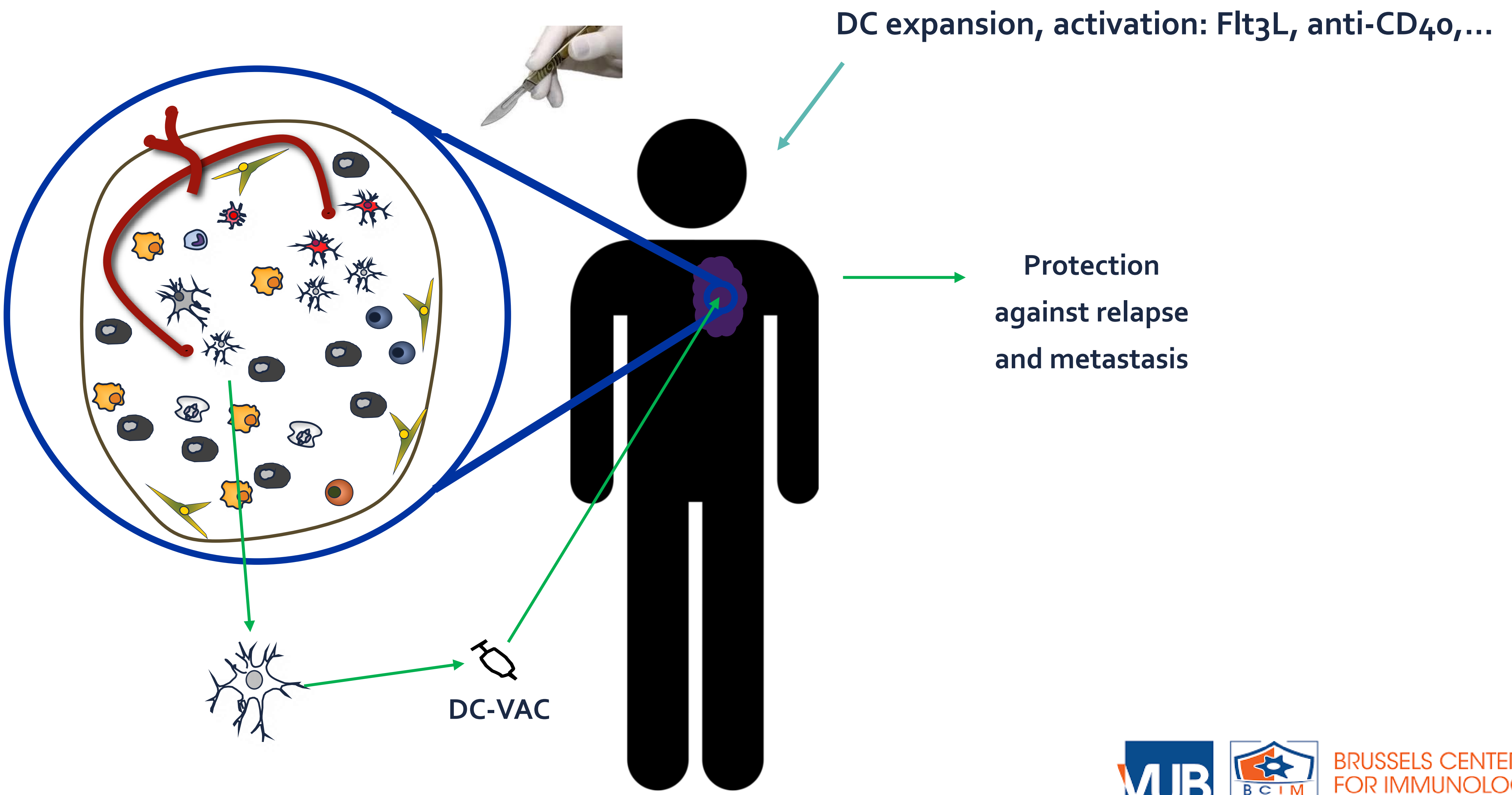
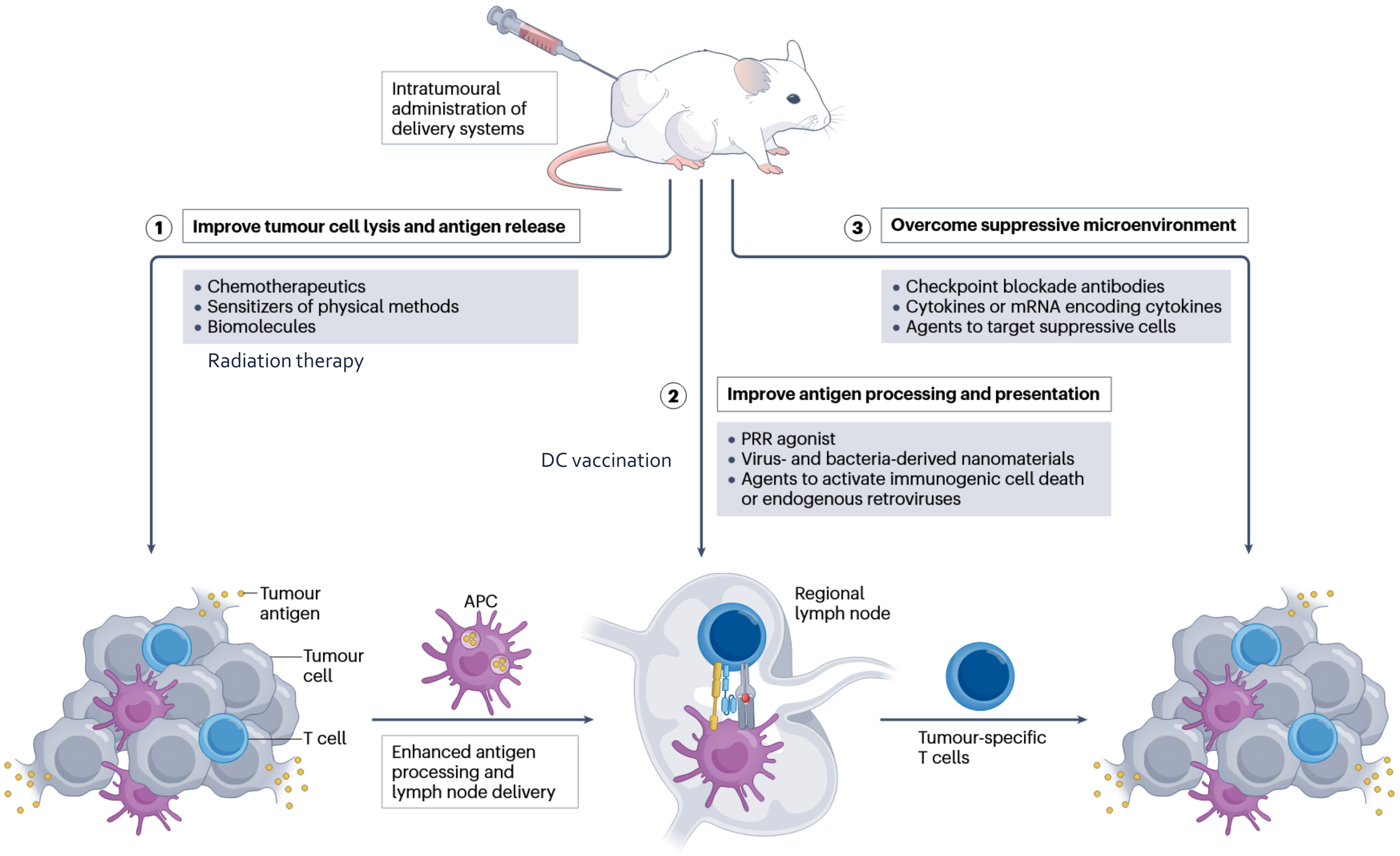


Combination therapies



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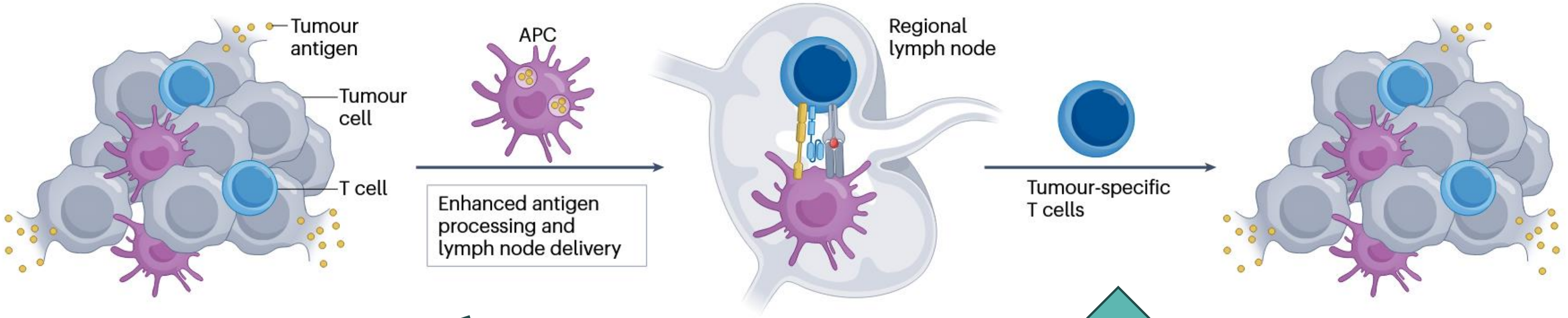
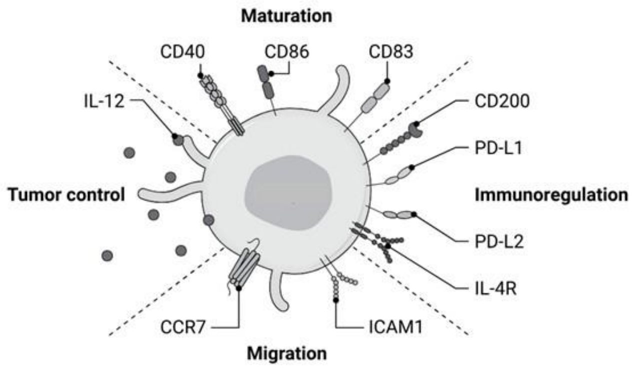
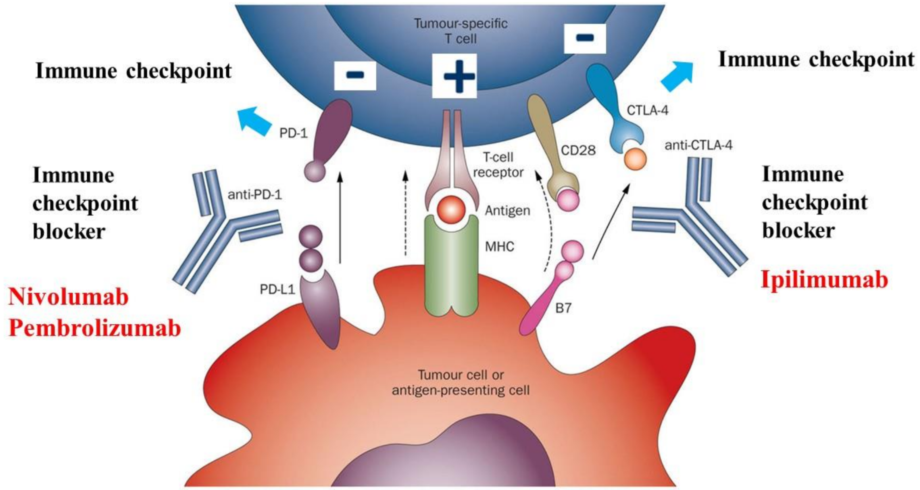
Combination therapies: DC vaccination + Immune checkpoint blockade







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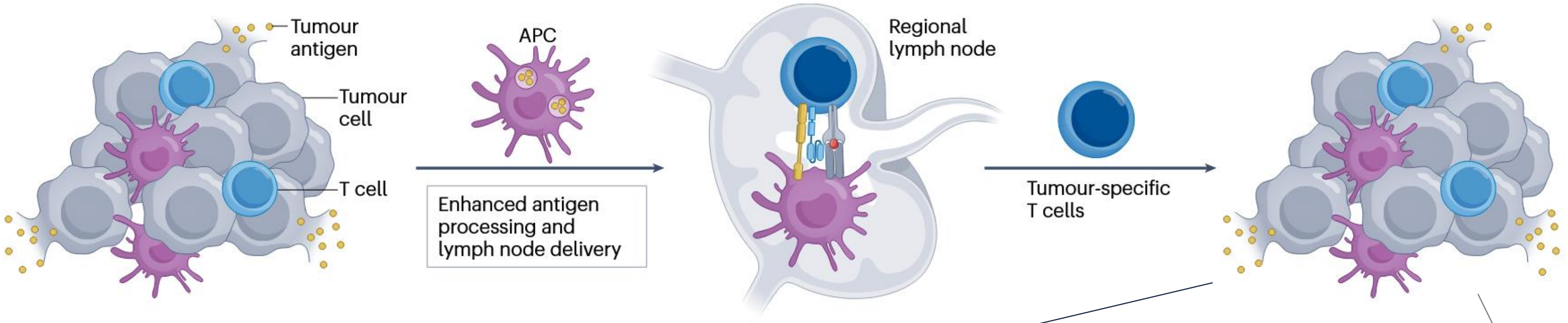
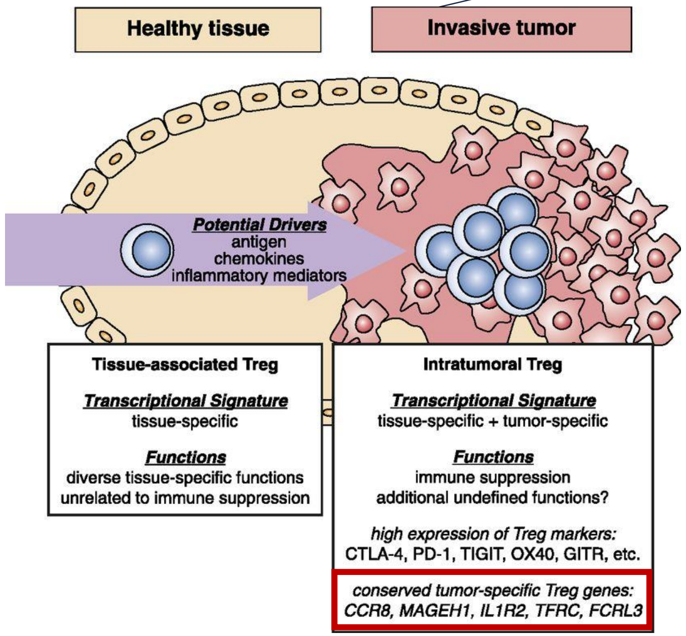
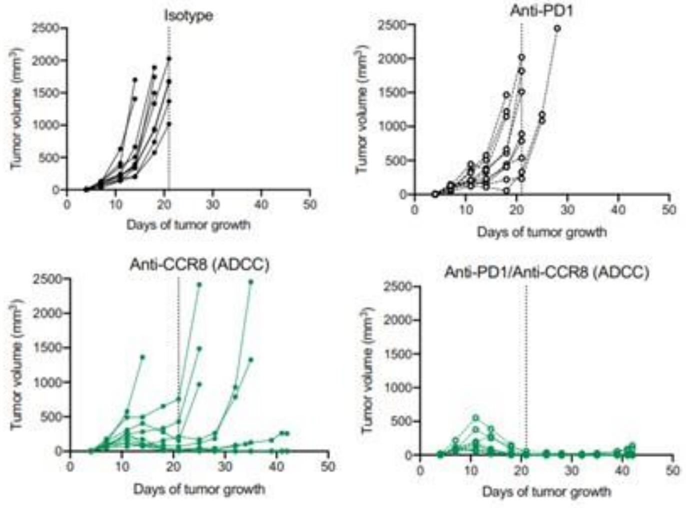
Combination therapies: Removal of immune suppressive tumor microenvironment



Removal of Tumor-infiltrating Treg





Anti-PD1 + anti-CCR8

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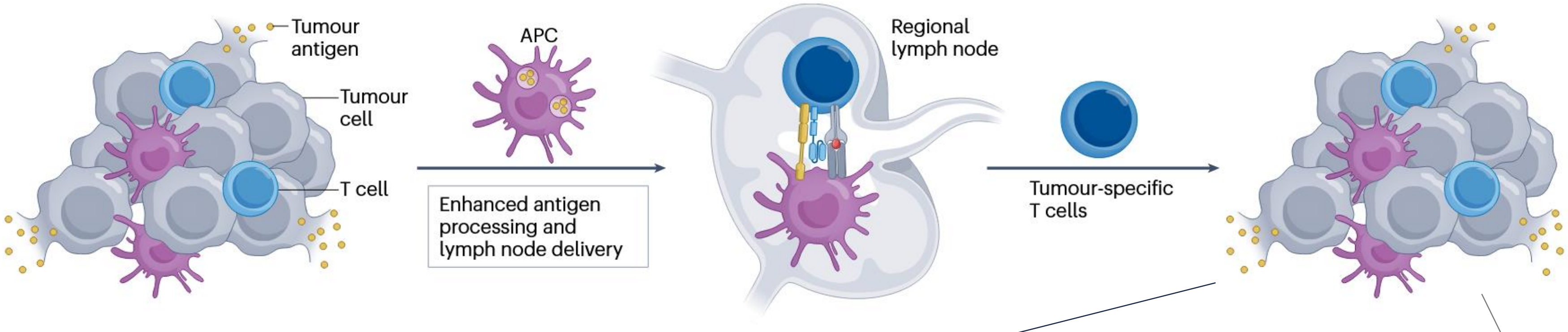
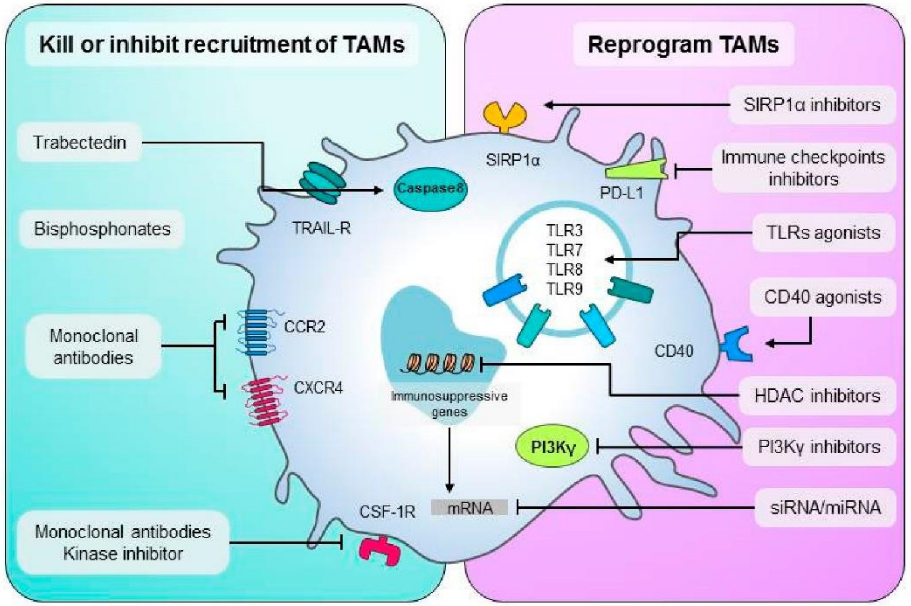
Combination therapies: Removal of immune suppressive tumor microenvironment



Removal or repolarization of tumor-infiltrating macrophages



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Acknowledgements

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VIB CENTER FOR INFLAMMATION RESEARCH

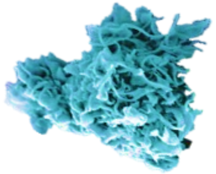
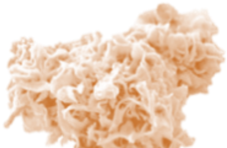
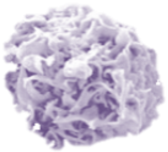
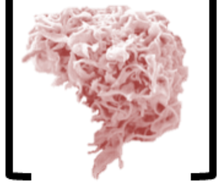
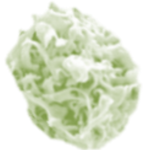
fwo

Kom op tegen Kanker

foundation against cancer

imi innovative medicines initiative

How to present tumor antigen to T cells?

	Conventional cDC1 	Conventional cDC2 	Plasmacytoid pDC 	LC 	Monocyte derived DC 
Ontogeny	HSC + Flt3-L, BATF3, BATF3, ZFP366, NFIL3 and Id2	HSC + Flt3-L, RelB, NOTCH2, RBP-J, IRF2 and IRF4 T-bet OR RORγt	HSC + Flt3-L and E2-2	Blood residing monocytes + inflammation	Fetal liver monocytes + CSF1R
Mouse Other markers	**$CD8\alpha^{+}/CD103^{+}$ cDC** $DEC205^{+}$	**$CD4^{+}$ $CD11b^{+}$ cDC**	**$SiglecH^{+}$ $BST2^{+}$ pDC** $B220^{+}$	**$Langerin^{+}$ LC**	**$CD11b^{+}$ moDCs** CD64, FcγRε, Ly6c
Human Other markers	**$CD141^{+}$** (BDCA-3) **cDC** $CD162^{hi}$ $DEC205^{hi}$	**$CD1c^{+}$** (BDCA-1) **cDC** $CD11b^{lo/+}$	**$CD123^{+}$ pDC** $BDCA\text{-}2^{+}$, $BDCA\text{-}4^{+}$	**$Langerin^{+}$ LC** DEC205, $CD1a^{hi}$	**$CD11b^{+}$ $CD1a^{+}$ moDCs** $CD24^{+}$, $CD206^{+}$, $CD16^{+}$ and DC-SIGN
Conserved (besides CD11c and MHC class II)	**$TLR3^{+}$ $CADM1^{+}$ $XCR1^{+}$ $CLEC9A^{+}$**	**$MHCII^{hi}$ $SIRP\alpha^{+}$ (CD172a)**	**$TLR7^{hi}$ $TLR9^{hi}$**	**$E\text{-}cadherin^{+}$, $EpCAM^{+}$, and $Langerin^{+}$**	**$CD11b^{+}$**
Functions	**T_H1 Cross-presentation**	**T_H2 and T_H17 Cross-presentation**	**IFN-α/β and IFNλ Humoral**	**Adaptable MOUSE: Treg or T_H17 HUMAN: IL-15 promoting CTLs + Cross-presentation**	**Highly adaptable (IL-12, IL-23, TNFα, iNOS)**

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