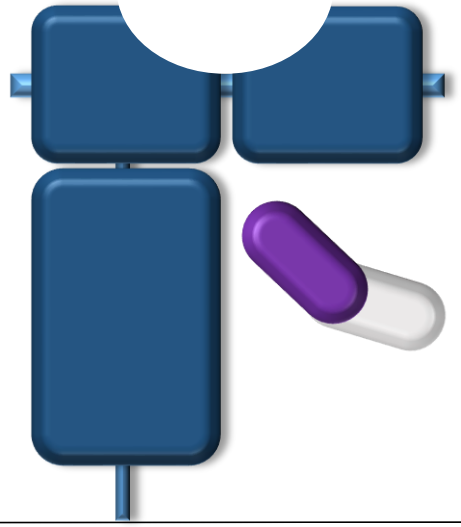
Why current vaccine approaches fail to reach the high-hanging fruit?



VACCINES RESEARCH AND DEVELOPMENT
November 18-20, 2019
Boston, USA

G. Vanden Bossche, DVM, PhD
Consultant Vaccine Research Collaborations

I see vaccines for all human and animal beings, and vaccines
preventing and treating infectious, malignant or immune-mediated diseases
And I think to myself…..
What a wonderful world!

Overview

- Introduction
- Vaccines & immune system: A huge potential?
- Current vaccines: An old lady in a modern dress?
- Are we heading in the wrong direction?
- Are we asking the right questions/ using the right antigens?
- Why we need *disruptive* innovation….
- Shifting gears…from an empirical to a ‘truly rational’ vaccine design…
- NK cells: The new Holy Grail in modern vaccinology?

frontiers in Endocrinology

Front Endocrinol (Lausanne). 2016; 7: 150. PMCID: PMC5256113
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doi: 10.3389/fendo.2016.00150

Autoimmune/Inflammatory Syndrome Induced by Adjuvants and Thyroid Autoimmunity

Abdulla Watad,[1,2,3] Paula David,[2,4] Stav Brown,[3] and Yehuda Shoenfeld[2,3,5,*]

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J Autoimmun. 2013 Dec;47:1-16. doi: 10.1016/j.jaut.2013.10.004. Epub 2013 Nov 13.

Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) 2013: Unveiling the pathogenic, clinical and diagnostic aspects.

Perricone C[1], Colafrancesco S, Mazor RD, Soriano A, Agmon-Levin N, Shoenfeld Y.

Author information

Immune system & Vaccines: A huge potential ?

Certainly! Unfortunately, progress is severely hampered by

- old dogmas ('conventional wisdom') and empiricism
- our lack of understanding of molecular mechanisms underlying

(i) immune pathogenesis of infectious and immune-mediated disease

(ii) immune subversive host-pathogen interactions

(iii) immune escape of pathogens to their host

The major issue of contemporary vaccinology: Lack of understanding of the ***immune pathogenesis*** of infection, malignant or immune-mediated disease

- Immunologists have learned a lot from vaccinologists but true learnings have rarely occurred the other way around
- Current 'progress' is largely based on new technologies and techniques including gene-based immunization and big data mining (-omics) rather than on a fundamental understanding of host-pathogen interactions and immune subversive mechanisms which pathogenic agents have evolved to escape natural mechanisms of host immune defense
- Increasing number of 'off target' studies and exercises in molecular stamp collection are slotting components into increasingly complex biochemical/ molecular pathways
- Increasing capacities, complex technologies and big data: ***Anyone still sees the forest for the trees?***

‘Novel’ vaccine approaches: An old lady in a *modern* dress?

Modern? ‘Yes, of course…’.

- Structural & computational modeling/ biology
- Bioinformatics
- Systems Biology
- Characterization of immune signatures/ signaling pathways
- Inventories of adjuvant signatures/ microarrays
- The era of –omics and data mining
- Development of exciting CAR-T cells & checkpoint inhibitors
- Personalized vaccinology
- Artificial intelligence

Ex.: “Human Vaccines Project” (to accelerate the development of vaccines and immunotherapies against major global infectious diseases and cancers by ***decoding the human immune system***)

‘Novel’ vaccine approaches: An *old* lady in a modern dress?

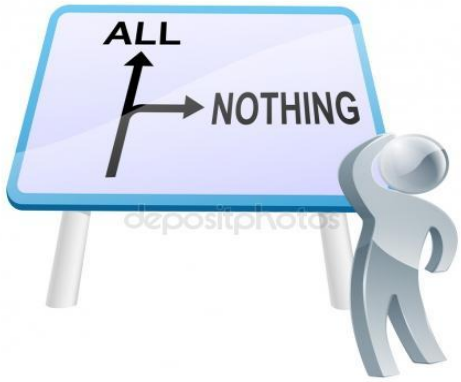
- Selection of vaccinal Ags largely relies on naturally induced immune responses that *correlate with recovery from acute disease by **specific** pathogens (Abs) and/* or *control of chronic disease in **genetically predisposed** subjects (T cells)*
- Still using antigens/ epitopes exposed on the *surface* of the free-circulating pathogens or presented on the *protein-binding groove* of cell surface-expressed *MHC* molecules
- Therefore, still inducing *foreign-centered* immune responses (B & T cells) that are *restricted by antigenic variability* of the pathogen and/ or by the *immuno-genetic background* of the host
- And thus, still inducing immune responses that are prone to *immune escape*
- Still focused on *protein/ polypeptide* Ags (even if delivered as DNA/ RNA/ mRNA etc.) *and adjuvants* (Th1/ 2/ 17 etc.)
- Still raising safety *concerns* related to hyper-inflammatory immune responses, immune pathology or exacerbation of disease
- Still using challenge models in animals that are *not naturally susceptible* to the pathogen to predict efficacy in naturally susceptible target species

Are we asking the right questions?

Resistance to fundamental but challenging questions prevents paradigm-shift in translational vaccinology:

- Are '*conventional' pathogen-derived antigens* adequate immunogens?
- Do we really need *multiple* antigens for broad strain coverage?
- Do we really need *different vaccines* for different pathogens (strains)?
- Do we really need multiple doses (→ slow onset)?
- Do we need higher doses to optimize the immune response? ('*The more the better'*?)
- Do we really need *adjuvants*?
- Why can't we make vaccines that not only prevent but also *cure* disease or protect against allergic or immune inflammatory disease?
- Are side effects and pain inevitable? (↔ '*no pain, no gain*'?)
- Are *'increasing complexity'* and *'personalized'* vaccines the right answer to current vaccine shortcomings?

Are we heading in the wrong direction?



What we (seem to) strongly believe in:

- Conventional Ags, adjuvants and foreign-centered immune responses
- Mimicking immunity that correlates with natural protection/ control of infectious disease
- 'Irrelevant' animal models
- High level of complexity
- Big data (-omics & mathematical modeling thereof)
- More resources, consortia, data (mining); more 'personalized' approaches

What we don't know, don't explore or don't seem to believe in:

- How the host immune system enables *pathogen replication or immune pathology at an early stage of infection or immune-mediated disease*?
- '*Relevant*' animal models
- *'One-size-fits-all':* One vaccine protects against *multiple* pathogens in *multiple* vertebrate species
- The power of *unconventional Ags* and *self-centered* immune responses

We care about compiling big dictionaries, not that much about speaking the language…

Example: - Omics

Freak-omics like to study *naturally or vaccine-induced* protective immune responses (or side effects):

- *Do they provide any key learnings on how to protect subjects against immune subversion caused by a different (type of) pathogen and/ or occurring in subjects with a different immunogenetic background (i.e., who are **not** genetically endowed with protective Ag-matching alleles)?*

Example: Adjuvants

- Adjuvants have their limitations and did not enable any breakthrough in vaccine efforts against the 'high-hanging fruit'

(Vanden Bossche G, Re-thinking Vaccinology. J Clin Immunol Res. 2017; 1(1): 1-3)

“Modern” (Tc-based) immune interventions have their limitations…

- Tumor Ag-reactive T cells are *neither necessary nor sufficient* for tumor rejection and raise interesting questions regarding the significance of T-cell responses against unmutated tumor antigens”

(“On the Role of Unmutated Antigens in Tumor Rejection in Mice with Unperturbed T-cell Repertoires; Sarma S. et al.; Cancer research 63, 6051–6055, 2003)

- Multi-epitope Tc vaccines protect individuals who are already naturally predisposed to Tc-mediated control of infection or disease by virtue of their protective alleles

(Hansen SG [2013], “Cytomegalovirus vectors violate CD8+ T Cell epitope recognition paradigms“; Science 340: 1-34)

- CAR-T cell therapies: Toxicity? Persistence? Resistance? Manufacturing? Cost?

- Understanding the Limitations of CAR-T Cell Therapies https://www.cancertherapyadvisor.com/home/cancer-topics/hematologic-cancers/cart-cell-therapy-cancer-limitations-treatment/

- Mechanisms of resistance to CAR T cell therapy (Nat Rev Clin Oncol. 2019 Jun;16(6):372-385)

- Ipilimumab and other so-called ‘checkpoint inhibitors’ do not work in everyone. They are only effective if the patient’s immune system already recognizes the cancer as the enemy; they have been reported to induce diarrhea and colitis

(“Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade”; McGranahan N. et al.; Science 351:1463-903, 2016; Immune-checkpoint Inhibitors : A Review of Incidence, Pathogenesis and Management; Hamzah A-S et al., Curr Opin Gastroenterol. 2019;36(1):25-32.)

We need *disruptive* innovation in vaccine design as conventional vaccines come with important limitations

LIMITATIONS

- Limitations in *coverage* of target pathogens (Ag variability/ variation) or target population (e.g., MHC-restriction!) and hence, in sustainability of efficacy at population level (immune escape!): ***No 'universal' vaccines*!**
- *No vaccines preventing infection or disease caused by multi-stage or cell-to-cell spreading pathogens*
- *No vaccines capable of abrogating infectious disease (no therapeutic value, useless during incubation of infection or during pandemic)*
- *No stand-alone vaccines for cancer or immune-mediated diseases*
- *Multiple shots („boost" or „prime-boost") required*
- ***Ag (peptides/ protein!) selection relies on immune correlates of natural protection applying to a specific (type of) pathogen and/or immuno-genetic background → overall* relevance of 'conventional' immune biomarkers of protection?**
- *Added value of alternative (conventional) Ag discovery? + resource- and cost-intensive, still empirical and subject to immune escape*
- *Protection in irrelevant animal models is not predictive of protection in target species*
- *Long vaccine development timelines: Emerging diseases??*
- *Safety concerns (immune pathology ~ use of adjuvants)*

Are current vaccines targeting the right antigens?

I have a dream that…..

most conserved & immune subversive pathogen-associated components would be exposed on the surface of freshly infected or otherwise pathologically altered cells

Huge missed opportunity for vaccines?

Such conserved, pathogen-associated immune subversive components do exist!

Pathogens have evolved to incorporate into their arsenal of peptides/ glycans self-mimicking motifs that are highly ***conserved,*** known to be part of ***vitally important*** proteins/ glycoforms, and exposed ***on the surface of infectious agents or on infected or otherwise pathologically altered host cells***.

These peptide Ags, however, are either ***immuno-silent*** or otherwise ***immune subversive*** (i.e., in case of infection, immune-mediated or malignant disease).
Hence, they are ***unconventional*** and do not qualify as target Ags for conventional vaccines!

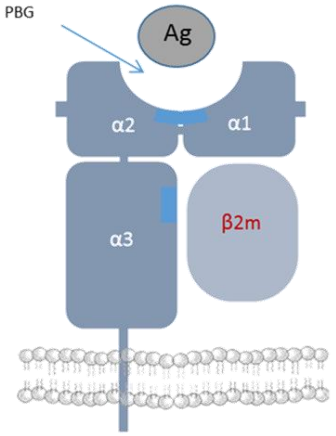
We consider that new vaccines enabling immune targeting of these Ags hold great promise for a multitude of prophylactic or therapeutic immune interventions (including 'high-hanging' fruits)

Pathogen-derived self-mimicking peptides* (PSMPs) mislead the host immune system

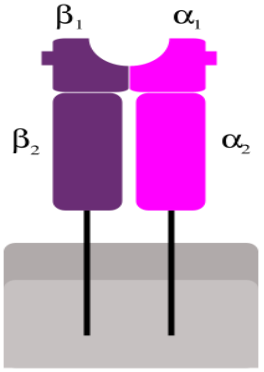
During evolutionary adaptation to their vertebrate hosts, pathogens incorporated into their arsenal of peptides one or more PSMPs sharing structural or functional homology with MHC-associated self-peptides (= self mimicry)

PSMPs are thought to bind to MHC molecules outside of a polymorphic MHC context, thereby preventing foreign Ag presentation while avoiding effective recognition of their β2m peptide-mimicking epitope by the host immune system

MHC cl I



MHC cl II



MHC-I: major histocompatibility complex class 1
PBG: peptide-binding groove

Immune escape ± immune pathology

*"Some mutated tumor-associated surface proteins that are bearing hallmarks of self-origin are shared by all of a patient's cancer cells" (in: Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade ; N. McGranahan et al. ; Science 25 Mar 2016: Vol. 351, Issue 6280, pp. 1463-1469)

*"Self-mimicking peptides on immunopathogenic proteins can be recognised by the host immune system regardless of host MHC polymorphism" in: Functional Analysis of Birch Pollen Allergen Bet v 1-Specific Regulatory T Cells - Toshihiro Nagato et al.; The Journal of Immunology, January 15, 2007, vol. 178 no. 2 1189-1198

PSMPs display structural or functional homology with conserved self-peptides associated with Ag-presenting/-processing molecules of naturally susceptible vertebrates

Pathogen-derived Self-Mimicking Peptides PSMPs

$_{266}$gtkyhlksg**hvtcevgl**eklkmkgl (**Dengue- Glycoprotein E**)

$_{131}$wfhiscltfg**retvl**eylvs (**hepatitis B- HBe**)

$_{804}$rsfiedllf**nkvtl**adagf (**SARS CoV-S2**)

$_{888}$saiedllfd**kvtiadp**gy (**MERS CoV-S2**)

$_{500}$ siefarlqftynhi**qrhvnd** **(Herpes Simplex -** gD**)**

$_{10}$tyvlsi**vpsgplk**aeiaqrledvfagkntdle (**Influenza** group A- M1)

myristoyl-$_{1}$dql**lwvsvfp** (**Rhinovirus** C **– VP4**)

myristoyl-$_{1}$mgmq**vstqkt** (human **Enterovirus – VP4**)

myristoyl-$_{1}$mgaq**vssqkv** (**Poliovirus – VP4**)

$_{141}$ge**tllrav**esyllahs (birch pollen **allergen-Betv1**)

$_{85}$srllefylam**pfatpme** (TAA: **NY-ESO-1**)

MHC-unrestr. binding site **(MUBS)**

in gray or green : PSMP epitope
in yellow: MUBS

β2m

$_{60}$wsfyllyyt$_{68}$-e**ftpte**kldeyac**rvnhvtlsqpk**$_{91}$

homologous β2m-derived self-peptides

Foreign peptides mimicking sequence-unrelated self-peptides may subvert the host immune system

Enhanced presentation of a pathogen-derived *foreign* peptide on the MHCII peptide-binding groove may enable recognition of multiple sequence-unrelated, *'foreign-mimicking'* self-peptides by T cells ('degeneracy' of TCR specificity*)

Table 2. Sequence Alignment of Viral/Bacterial Mimicry Peptides That Stimulate MBP-Specific T Cell Clones That Are DQ1 or DR2 Restricted

Peptides Recognized by Clone Hy.1B11 (DQ1 Restricted)

	85	90	94	99
MBP(85–99)	E	N	P	V V H F F K N I V T P R
Herpes simplex, UL15 protein	F	R	Q	L V H F V R D F A Q L L
Adenovirus type 12, ORF	D	F	E	V V T F L K D V L P E F
Pseudomonas, phosphomannomutase	D	R	L	L M L F A K D V V S R N
Human papillomavirus type 7, L2 protein	I	G	G	R V H F F K D I S P I A

(Cell. 1995 Mar 10;80(5):695-705. Molecular mimicry in T cell-mediated autoimmunity: viral peptides activate human T cell clones specific for myelin basic protein)

* Linda Wooldridge et al.; A Single Autoimmune T Cell Receptor Recognizes More Than a Million Different ; November 18, 2011 - J. Biol. Chem. 2012, 287:1168-1177

* Sunil K. Joshi et al.; Flexibility in MHC and TCR Recognition: Degenerate Specificity at the T Cell Level in the Recognition of Promiscuous Th Epitopes Exhibiting No Primary Sequence Homology; The Journal of Immunology, 2001, 166: 6693–6703.

* Christine Loftus et al.: Highly Cross-Reactive T Cell Responses to Myelin Basic Protein Epitopes Reveal a Nonpredictable Form of TCR Degeneracy; J Immunol 1999; 162:6451-6457;

Examples of PSMPs comprised within tumour-associated proteins

Cancers hold within them the seeds (i.e., self-mimicking features) of their own destruction...!. https://www.theguardian.com/science/2016/mar/03/genetics-of-cancer-tumours-reveal-possible-treatment-revolution

- PSMP derived from Mage A-1 tumour-associated protein (DBSOURCE UniProtKB: locus MAGA1_HUMAN, accession P43355):

231**hsaygeprkll**-**tqdlvq**e

- human β2m-derived self-peptide: 60wsfyllyyteftptekdeyacrvnh**vtlsq**pk
- human MHC-Ibα-derived self-peptide: 172**seaehqraylle**dtcvewlh

TAA: Tumor-associated antigen

PSMP from HIV

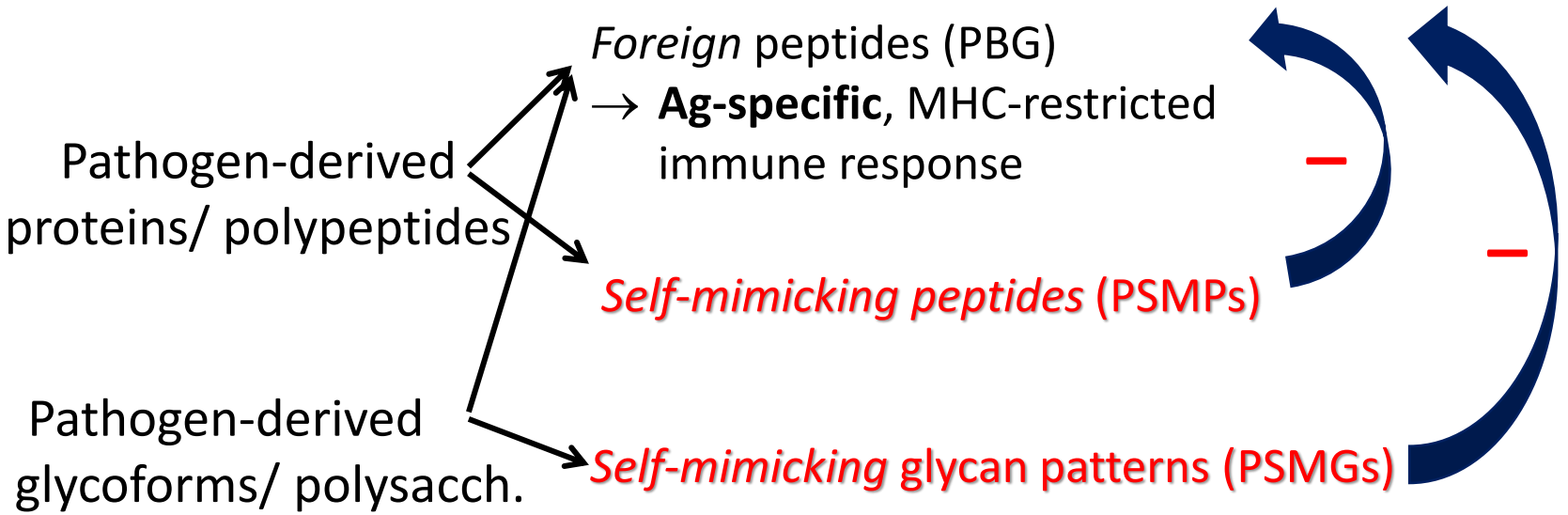
Example HIV virus

- PSMP derived from HIV Gag p24 protein (DBSOURCE accession AF025718.1):

  $_{14}$alsprtlna-wvkveekafnp

- human β2m-derived self-peptide: $_{60}$wsfyllyyteftptekdeyacrvnhvtlsqpk
- human MHC-Iaα-derived self-peptide: $_{1}$mavmaprtlvllls (= leader signaling peptide; LSP)

We are unlikely to catch the 'high-hanging' fruit as long as we ignore PSMP/ PSMG-mediated immune subversion



→ **Pathogen-nonspecific** immune silencing or subversion

– : Immune silencing/subversion occurs due to competition of PSMPs with MHC-associated self-peptides or due to competition of PSMGs with SAMP-binding self-glycans that are critical to antigen presentation or immune modulation, respectively

Shifting gears: How to induce *broadly and universally* protective immune responses towards pathogen-associated cell surface-expressed self-mimicking motifs?

- Presentation of corresponding *self-motifs* in a highly repetitive pattern (i.e., 'altered self' pattern) enables licensing of host NK cells to recognize and *target mutliple foreign (*pathogen-derived), sequence-unrelated self-mimicking motifs *on the surface of microbial cells or on the surface of infected or diseased vertebrate cells*
- *Multiple PSMPs a/o PSMG patterns can be recognized by adequately educated MHC-unrestricted NK cells*
- By targeting PSMPs a/o PSMG patterns, NK cells have the capacity to counter evolutionary adaptation and prevent immune escape of multiple (all?) pathogenic agents

Foreign peptides mimicking sequence-unrelated self-peptides may subvert the host immune system

Enhanced presentation of certain foreign (pathogen-derived) peptides on the MHCII peptide-binding groove may enable recognition of multiple sequence-unrelated, *'foreign-mimicking'* self-peptides by T cells ('degeneracy' of TCR specificity*)

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Peptides Recognized by Clone Hy.1B11 (DQ1 Restricted)

	85 90 94 99
MBP(85–99)	ENPVVHFFKNIVTPR
Herpes simplex, UL15 protein	FRQLVHFVRDFAQLL
Adenovirus type 12, ORF	DFEVVTFLKDVLPEF
Pseudomonas, phosphomannomutase	DRLLMLFAKDVVSRN
Human papillomavirus type 7, L2 protein	IGGRVHFFKDISPIA

(Cell. 1995 Mar 10;80(5):695-705. Molecular mimicry in T cell-mediated autoimmunity: viral peptides activate human T cell clones specific for myelin basic protein)

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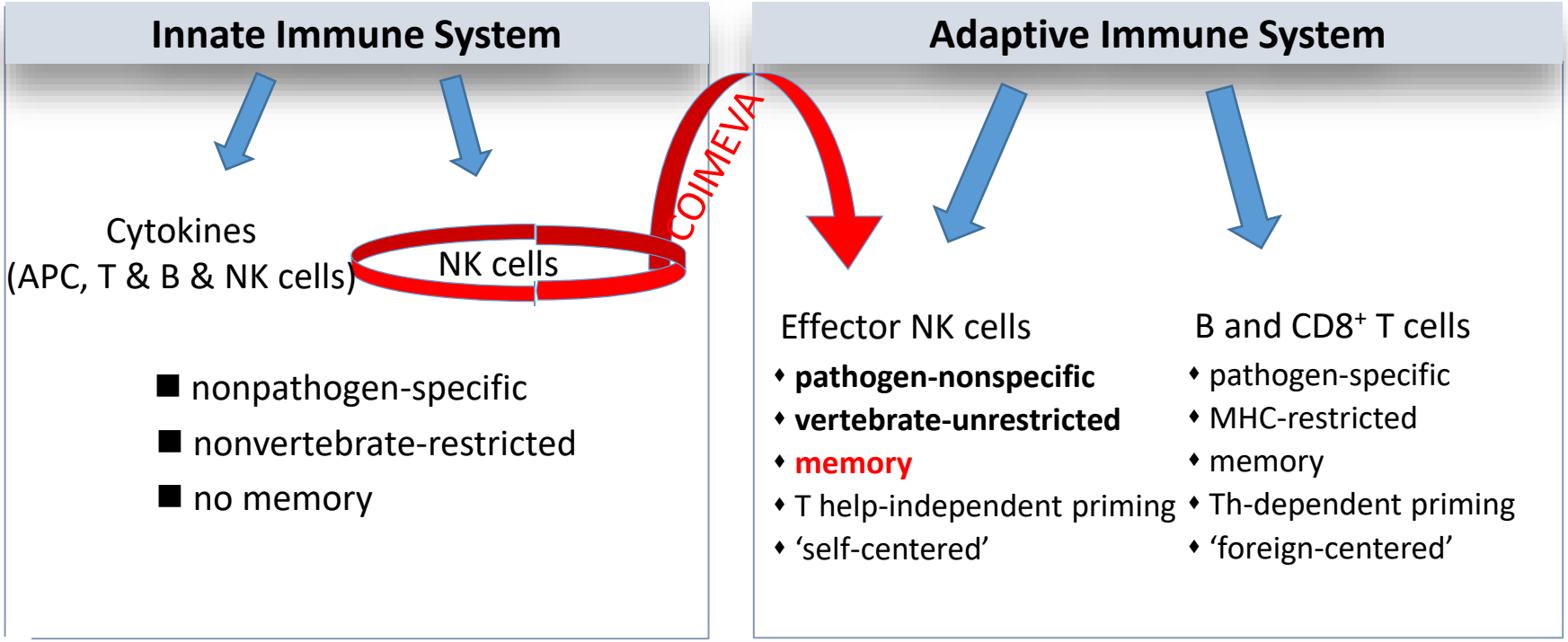
Self-based vaccines teach NK cells to combine features of innate and adaptive immunity

Signalling by non-self patterns of nonimmunogenic self-motifs educates innate host NK cells to serve a ‘universal’ adaptive immune function



NK cell-based vaccines: The new Holy Grail in Modern Vaccinology?

Review Article

Journal of Clinical Immunology & Research

Re-thinking Vaccinology: "Act Universally, think NK Cells"?

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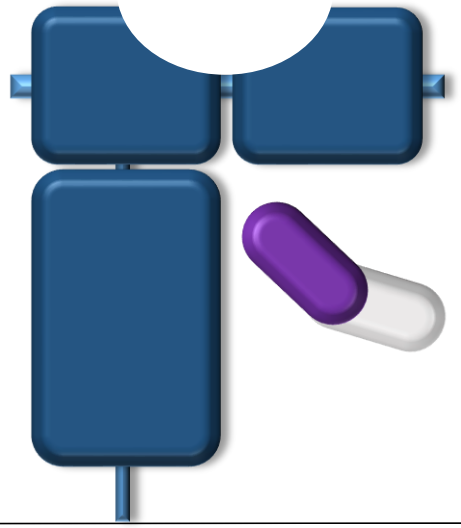
Thank you for your attention



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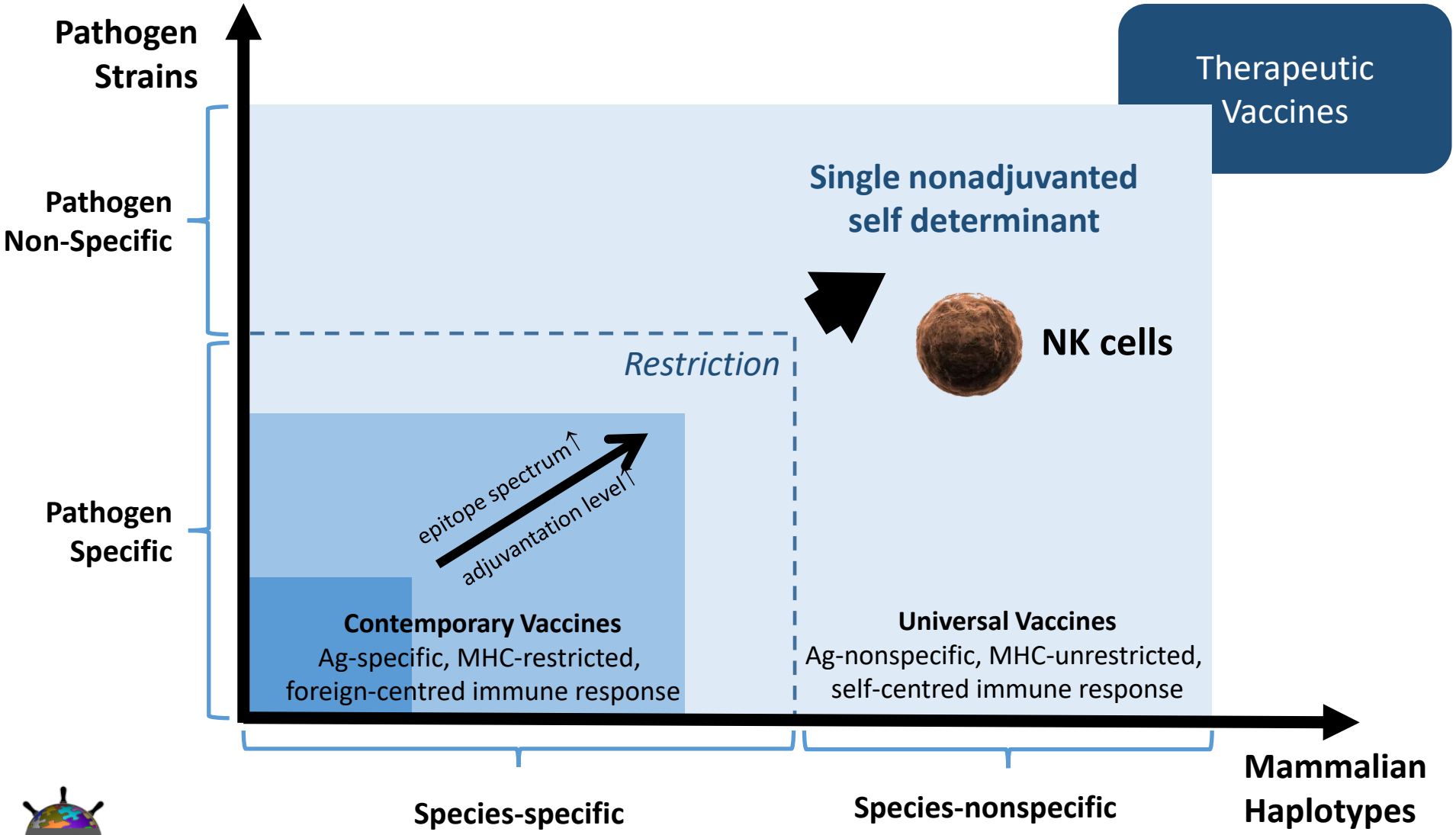
Shifting from foreign- to self-centred immune recognition enables unprecedented vaccine coverage



PSMPs compromise immune recognition of pathogen-derived peptides while *hiding* from the host immune system by mimicking β2m-derived self peptides

Example Influenza virus:

- Target peptide derived from Flu-M1: $_{10}$tyvlsi ipsgplkaeiaqr ledvfagkntdle

  - Human β2m peptide: $_{81}$sfyllyyteftptekdeyacrvnhvtlsqp
  - Porcine β2m peptide: $_{81}$sfyllvhteftpnavdqyscrvkhvtldkp
  - Ovine β2m peptide: $_{81}$sfyllshaeftpnskdqyscrvnhvtltqpk
  - Human MHCIb-α peptide: $_{171}$aseaehqraylledtcvewlh

self-peptide hapten

ex: MHC I