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European Business Development Conference
Dresden - October 7/8, 2014

Immuno-Oncology: Cancer Therapies Powered by the Immune System

Dr. Marlies Sproll, CSO

Power of the Immune System
Vaccination as Success Story

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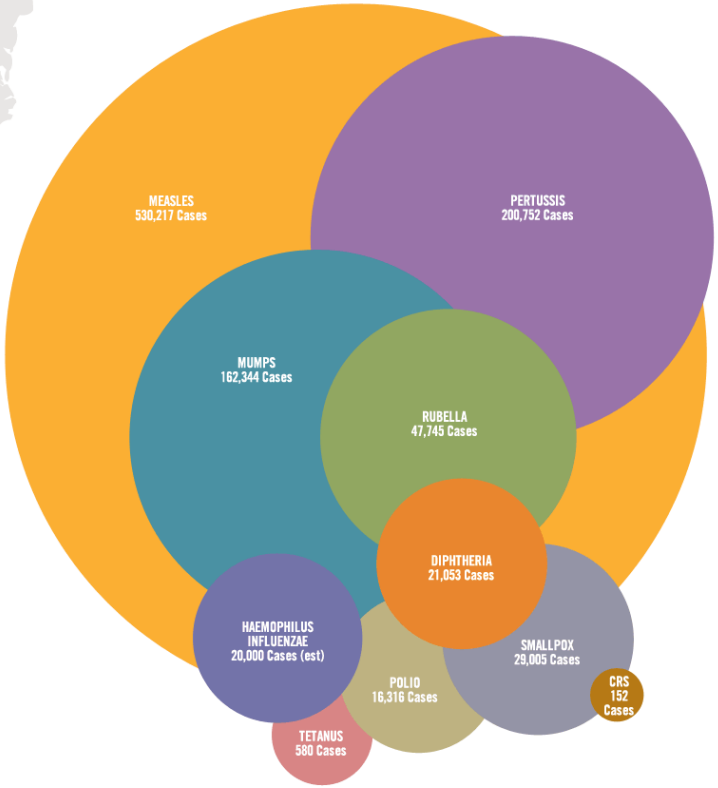
VACCINES WORK

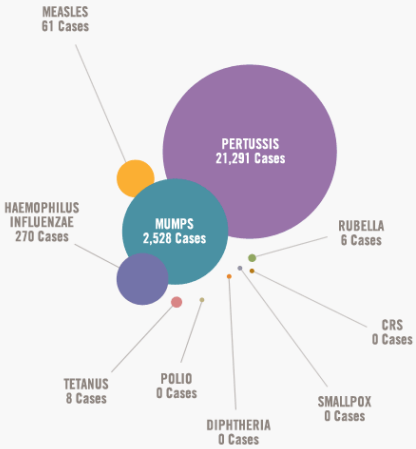
These bubbles are sized according to the annual number of disease cases in the US during the 1900s versus 2010. We've come so far. It's a reminder that while disease rates are low, most diseases haven't disappeared. This is why we continue to vaccinate.

	THEN	NOW
SMALLPOX	29,005	0
MEASLES	530,217	61
DIPHTHERIA	21,053	0
MUMPS	162,344	2,528
PERTUSSIS	200,752	21,291
RUBELLA	47,745	6
TETANUS	580	8
CRS	152	0
POLIO	16,316	0
HAEMOPHILUS INFLUENZAE	20,000	270

THEN
Annual US disease cases in the 1900s



NOW
US disease cases in 2010



[9] Centers for Disease Control and Prevention (CDC). Parents Guide to Childhood Immunizations. http://www.cdc.gov/vaccines/pubs/parents-guide/default.htm. Accessed August 15, 2011.
[10] CDC. Impact of Vaccines in the 20th & 21st Centuries. http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/G/impact-of-vaccines.pdf. Updated January 2011. Accessed August 15, 2011.

Source: http://sciencebasedpharmacy.wordpress.com/2013/05/12/vaccines-work-by-the-numbers/

Milestones in Cancer Immunotherapy
From History to Future

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1890s — **W. Coley** Used live bacteria (Coley's toxin) as anti-cancer vaccine

1900 — **P. Ehrlich** Molecules within the body migh have the abiltiy to fight tumors

1957 — **Burnet** Presence of antigens on the surface of tumor cells may induce an immune response leading to clinical manifestation

1965 — **Interleukin-2 (IL-2)** first discovered

1970 — **Morton** Described marked tumor regression after injection of BCG vaccine (melanoma)

1975 — **Köhler & Milstein** Nobel Price for development of monoclonal antibody technology

1986 — **First monoclonal antibody** approved by FDA

1986-2000 — Approvals granted for use of **interferons (IFNs)** and **IL-2** for treatment of neoplasias

1988 — Human cytotoxic T-lymphocyte associated antigen-4 gene (**CTLA4**) cloned

1991 — Isolation and cloning of the first human **tumor associated antigens** (TAA) from melanoma patients

1997 — FDA approval for use of **rituximab** as single agent in NHL

2002-2007 — Phase I-III trials carried out using **anti-CTLA-4 mAb**

2008 — **Provenge** - 1st therapeutic cancer vaccine approved by FDA (prostate cancer)

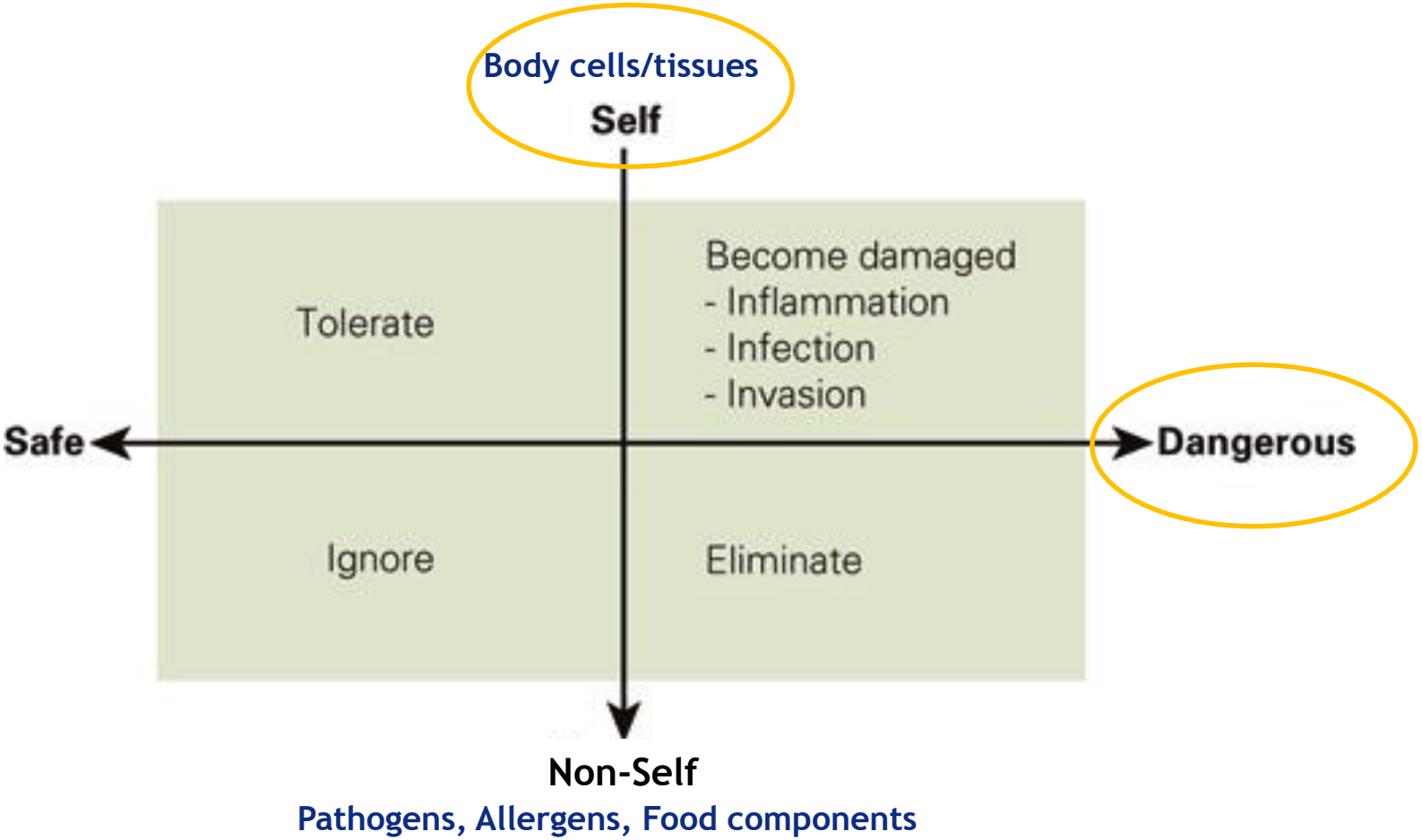
2008 — Hunder et al infused **autol. CD4+ T-cells** (NY-ESO-1) into a patient with refract. met. melanoma. Patient showed complete tumour regression

Bristol-Myers Squibb

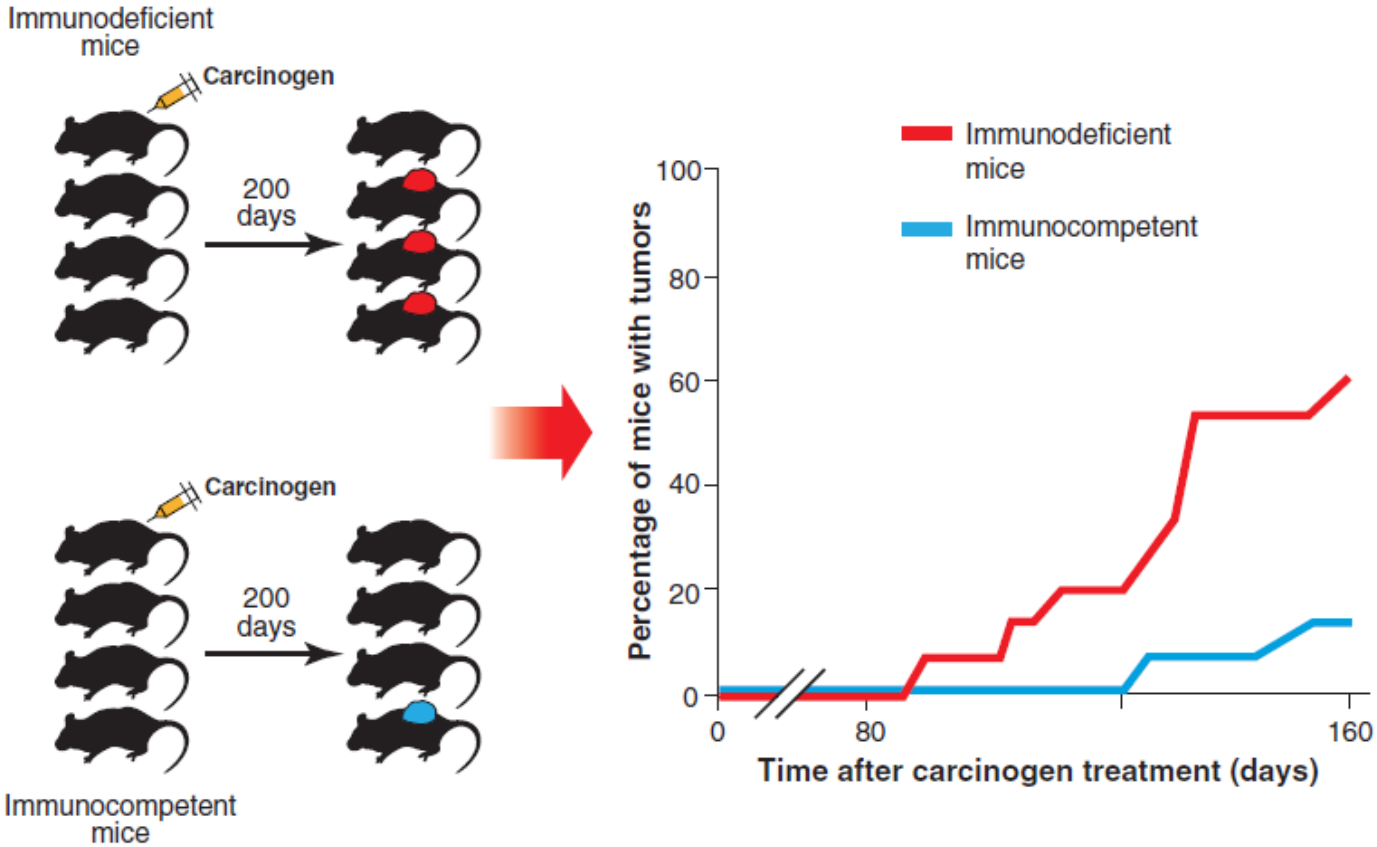
General Principles – YIN & YANG

Self/Non-Self versus Danger Model

- Constant integration of self vs. non-self and danger signals
- Decision between tolerance/ignorance and attack

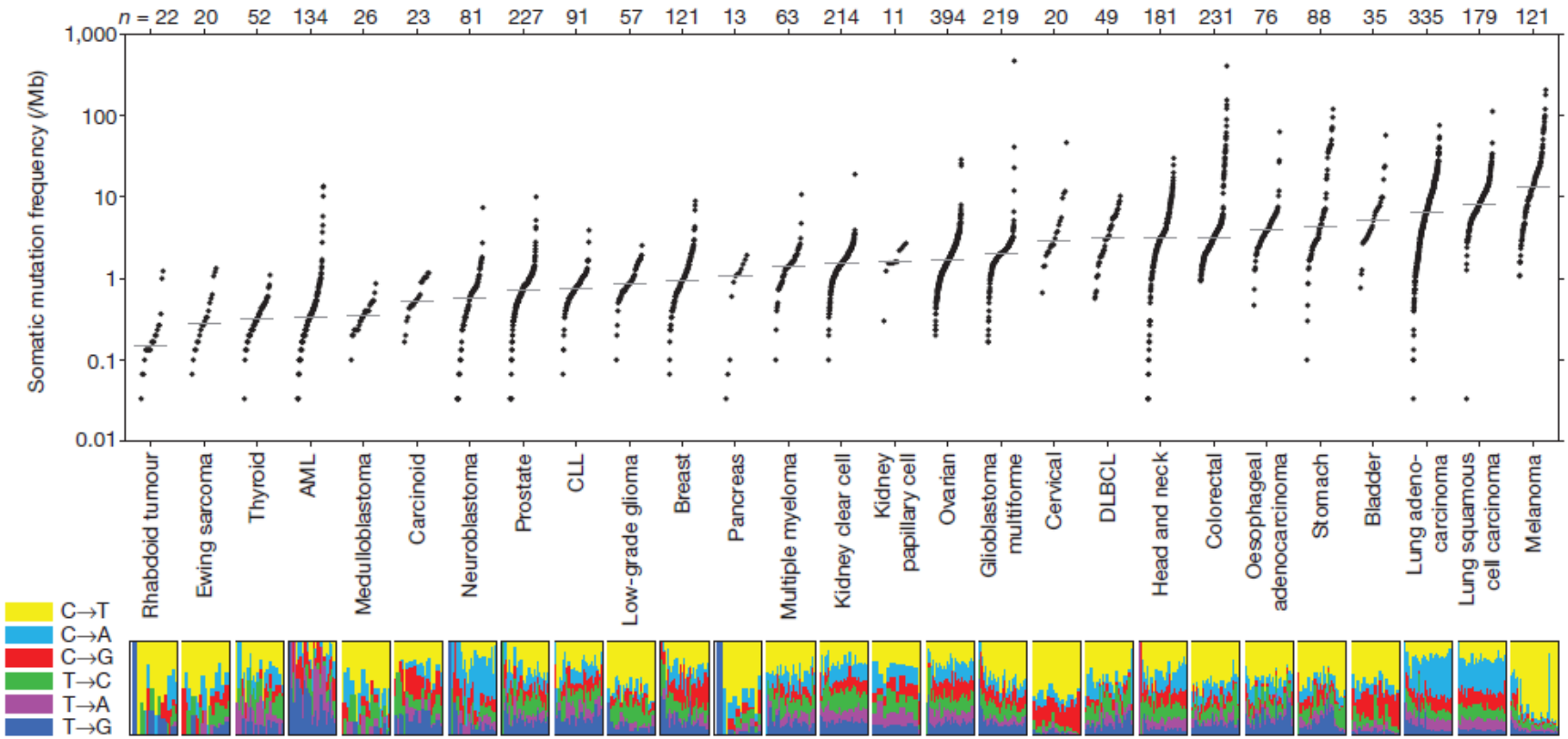


Immune System – A Capable Tumor Suppressor



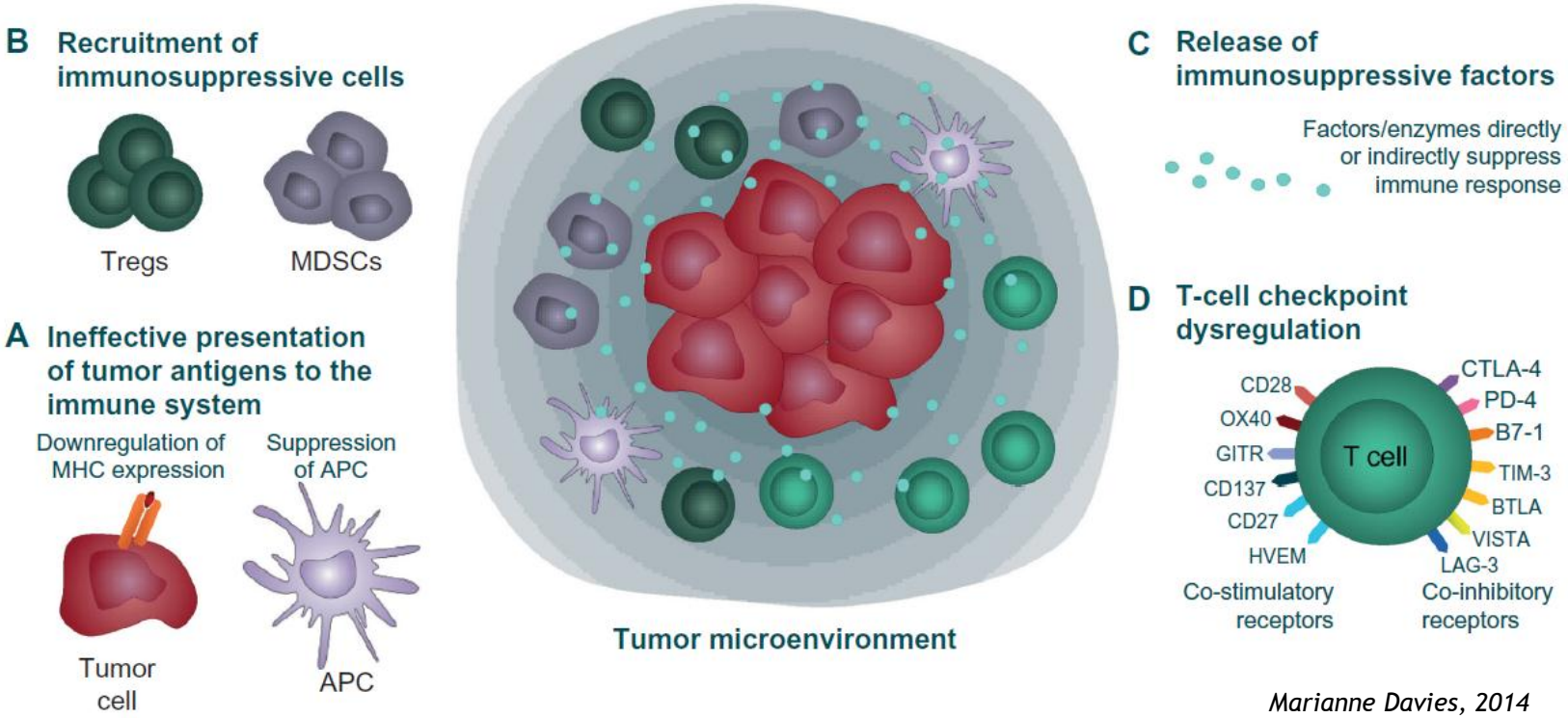
Schreiber et al. Science 2011

Challenges -
Mutational Burden / Heterogeneity of Tumors



Lawrence et al., Mutational heterogeneity in cancer and the search for new cancer-associated genes, Nature, Vol 499, 2013

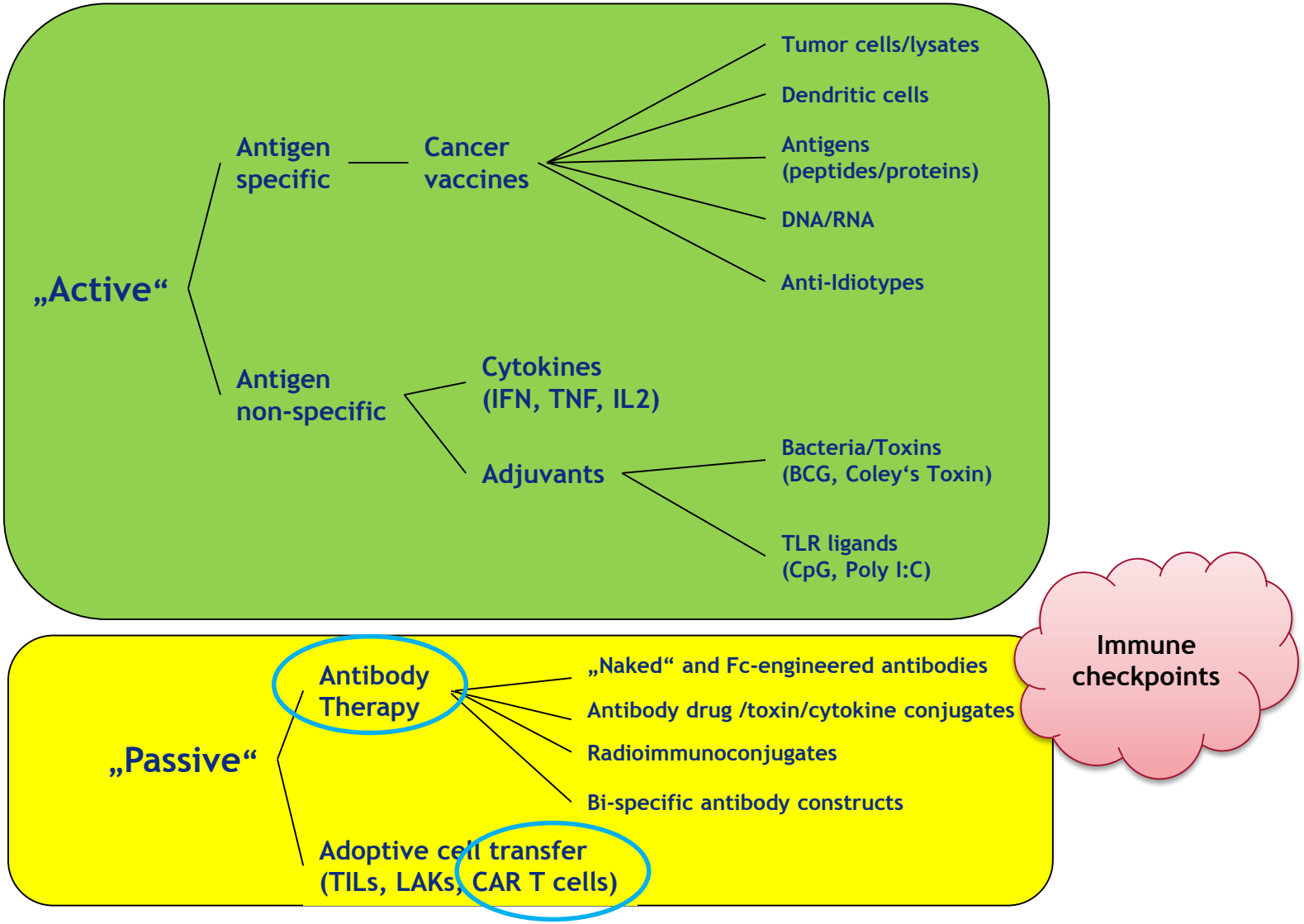
Tumor Cells Use Immunosuppressive Strategies to Evade Immune Responses



Marianne Davies, 2014

Cancer Immunotherapy Tool Box

Active vs. Passive Immunization



Immune Checkpoints

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Proteins regulating the amplitude and the quality of an immune response

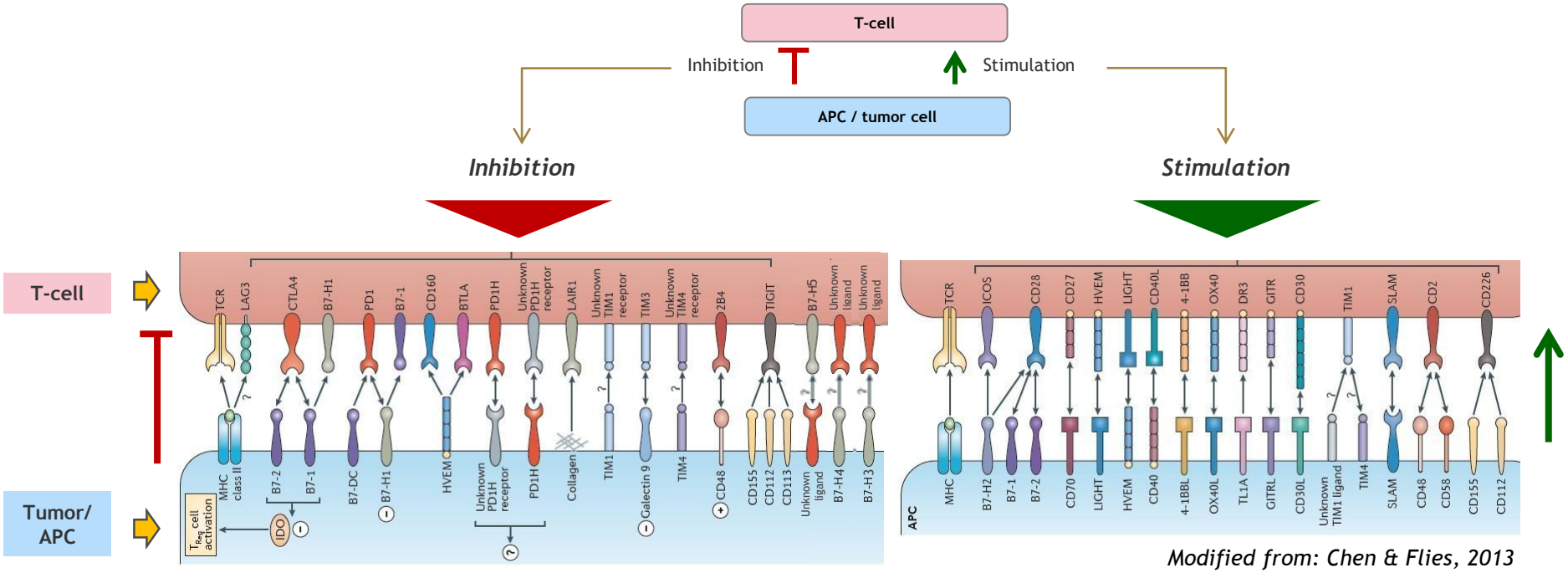
Co-stimulatory and co-inhibitory signaling molecules/receptors regulating T cell response

Crucial for the maintenance of self-tolerance (prevention of autoimmunity)

Protects tissue from damage when the immune system is responding to pathogenic infection

Can be dysregulated by tumors as an important immune resistance mechanism

T Cell Activation is Regulated by Co-Inhibitory and Co-Stimulatory Molecules

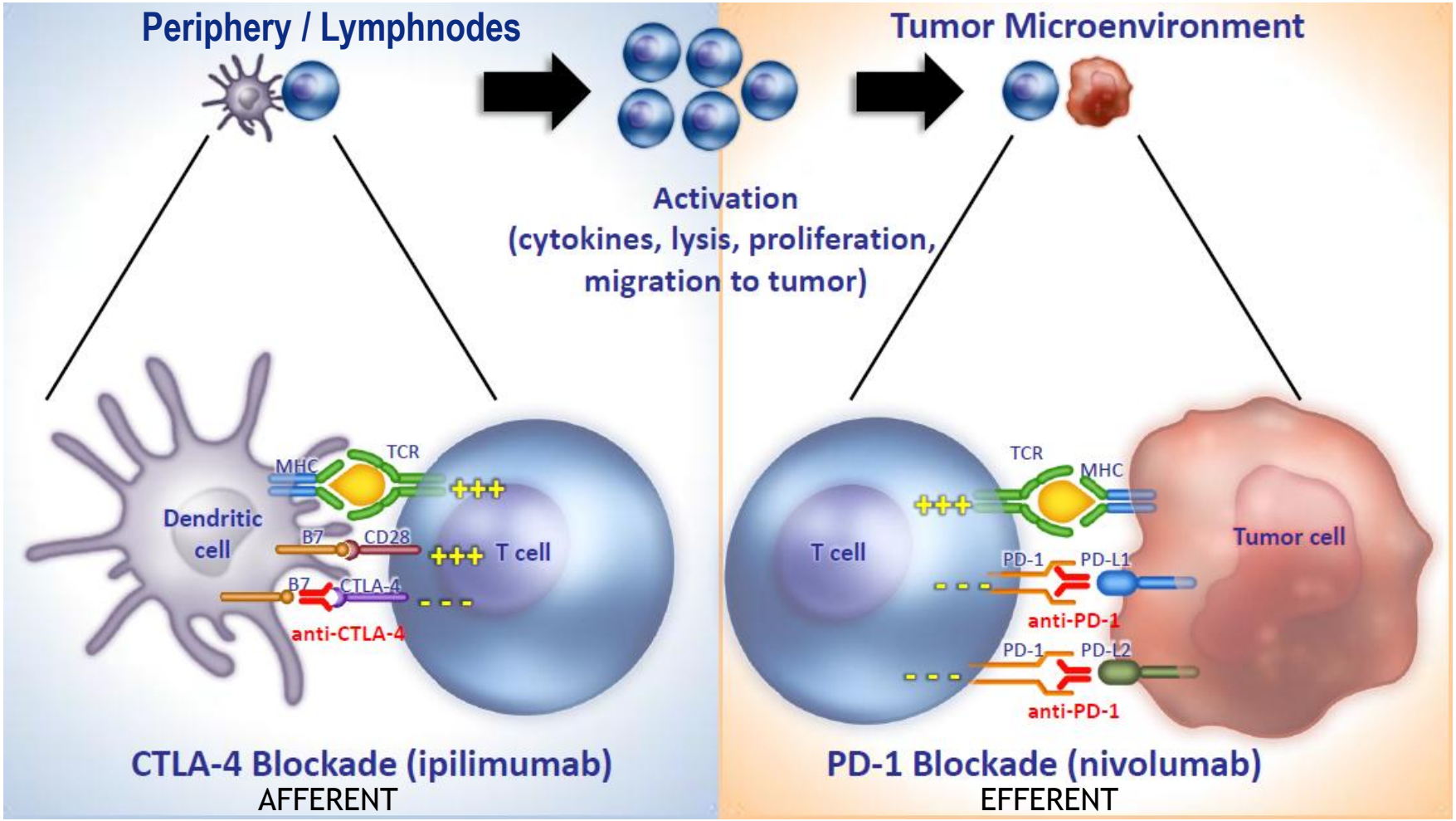


Modified from: Chen & Flies, 2013

- Cell cycle inhibition
- Inhibition of effector functions
- Tolerance
- Exhaustion
- Apoptosis

- Proliferation
- Cytokine production
- Differentiation
- Cytotoxic function
- Memory formation
- Survival

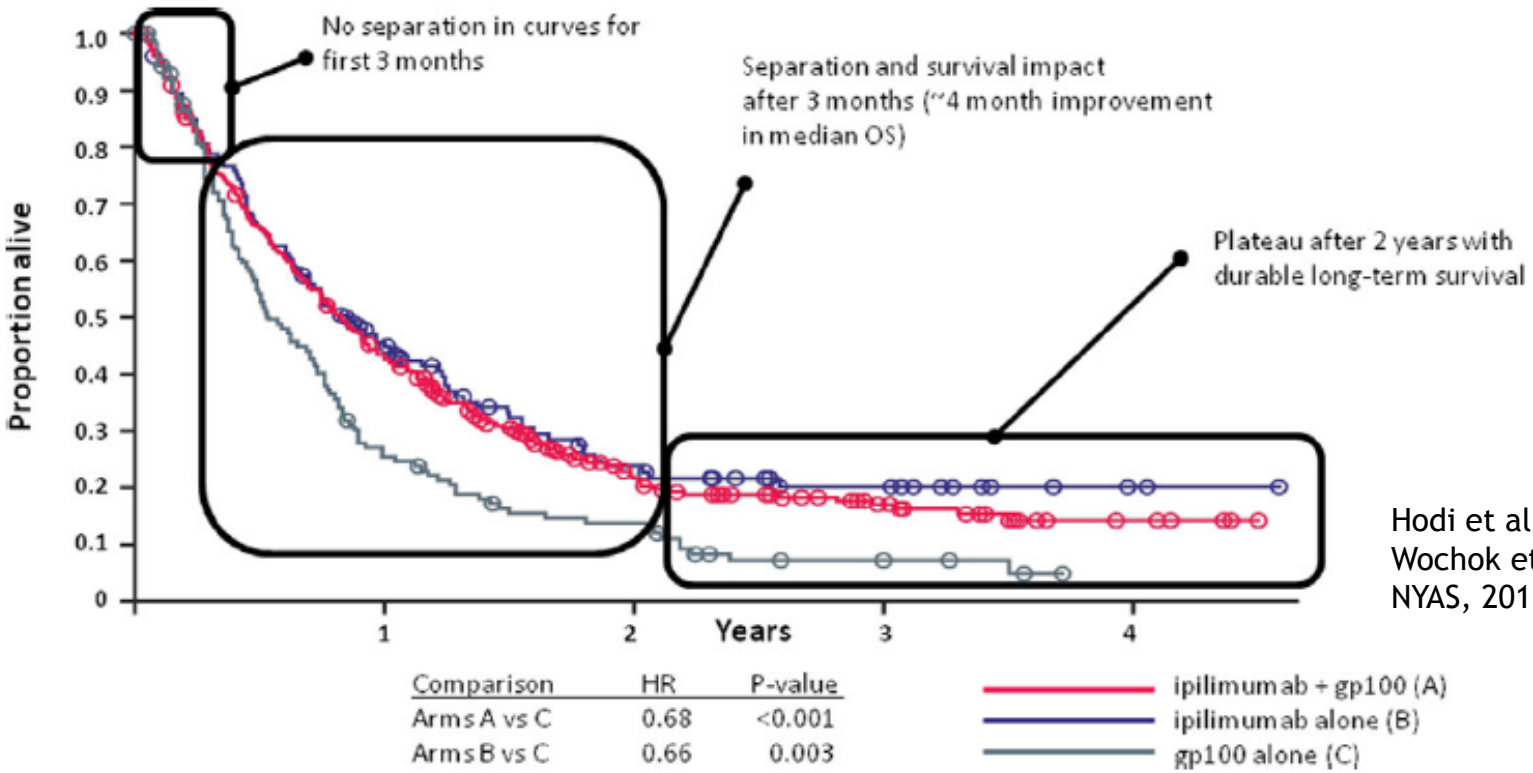
Complex Intercellular Communication at Different Sites



Source: Wolchock, J. et al, JCO 2013, Volume 31, Issue 15, Supplement

Yervoy – ipilimumab (anti-CTLA-4)

- **Astonishing long-term survival data in melanoma patients elicits enthusiasm for immuno-oncology approaches**



Hodi et al., NEJM, 2010
Wochok et al., Ann NYAS, 2013

- ongoing further development in e.g. NSCLC, SCLC, prostate cancer

CTLA-4
The Yin and Yang of T-Cell Regulation

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CTLA-4 knock-out mice (Waterhouse et al., Science 1995)

- Normal at birth
- Death within few weeks: massive multi-organ T cell infiltration
- CTLA-4 acts as a negative regulator of T-cell activation and is vital for the control of lymphocyte homeostasis

CTLA-4 deficient mouse strains (Tivol et al., Immunity 1995)

- Positive and negative roles for CTLA-4 in T cell activation shown by blocking antibodies
- CTLA-4 deficient mice rapidly develop lymphoproliferative diseases with multiorgan lymphocytic infiltration and tissue destruction, with particularly severe myocarditis and pancreatitis
- CTLA-4 deficient mice die by 3-4 weeks of age

CTL-A4 blockade in cancer patients

- Impressive anti-tumor responses but at the price of significant side effects

Next Imminent Wave

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- **anti-PD-1 antibodies**
  - believed to more "proximal" block immunosuppression compared to anti-CTLA-4; less serious side effects
  - ➢ Front running molecules:
    - **Opdivo nivolumab** (human IgG4; BMS / Ono) – approved in Japan 07/14 for unresectable melanoma; treatment costs $ 181,921 p.a.
      Under review EMA & FDA; PhIII interim data Non-small Cell Lung Cancer
    - **Keytruda pembrolizumab** (humanized IgG4; Merck & Co.) – FDA approval 09/14 for advanced melanoma; 24% of patients dosed at recommended dose of 2mg/kg every 3 weeks had tumor shrinkage; treatment costs $ 150,000 p.a.
- **anti-PD-L1 antibodies**
  - blocking PD-L1/PD-1 Interaction
  - additional blockade of PD-L1-B7.1 interaction
  - ➢ Front running molecules:
    - RG-7446/MPDL3280A (hu IgG1; Roche/Genentech)
    - MEDI-4736 (hu IgG1; MedImmune/AstraZeneca)
    - in mid stage clinical development, various cancer types

Immunomodulatory Antibodies in Clinical Development

Table 3. Immunomodulatory antibodies in clinical development.

Target	Antibody	Species	Isotype	Predicted ADCC	Company
CTLA-4	Ipilimumab	Humanised	IgG1	Yes	Bristol-Myers Squibb
	Tremelimumab	Humanised	IgG2	No	AstraZeneca/Pfizer
PD-1	Nivolumab	Humanised	IgG4	No	Bristol-Myers Squibb
	Pembrolizumab (formerly lambrolizumab)	Humanised	IgG4	No	Merck
	Pidilizumab	Humanised	IgG1	Yes	Cure-Tech
PD-L1	BMS-936559	Humanised	IgG4	Yes	Bristol-Myers Squibb
	MPDL3280A	Humanised	IgG1	No[a]	Roche
	MEDI4736	Humanised	IgG1	Yes	AstraZeneca
B7-H3	MGA271	Humanised	IgG1	Yes[b]	MacroGenics
OX-40	MEDI6469	Humanised	IgG1	Yes	AstraZeneca
4-1BB	Urelumab	Humanised	IgG4	No	Bristol-Myers Squibb
	PF-05082566	Humanised	IgG2	No	Pfizer
GITR	TRX518	Humanised	IgG1	No[a]	TOLERx
CD27	CDX-1127	Humanised	IgG1	Yes	Celldex
CD40	CP-870,893	Humanised	IgG2	Yes	Pfizer
	Lucatumumab	Humanised	IgG1	Yes	Novartis
	Dacetuzumab	Humanised	IgG1	Yes	Seattle Genetics
	Chi Lob 7/4	Chimeric	IgG1	Yes	Univ. of Southampton

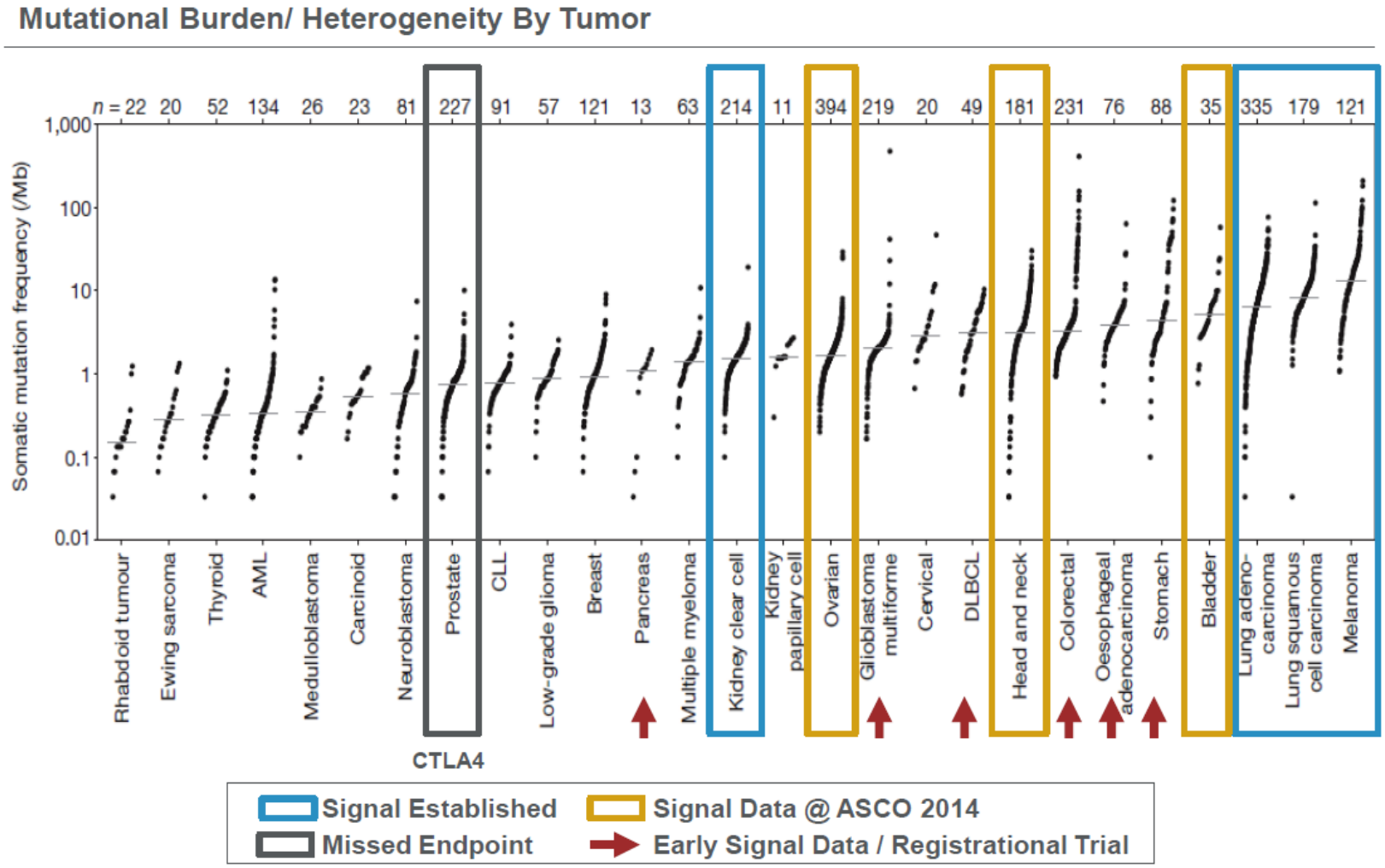
[a]Glycoengineered to abrogate Fc functionality.

[b]Glycoengineered to enhance ADCC.

Source: Furness et al, Trends in Immunol, 2014

- Increasing number of molecular targets on various cell types
- Various mechanisms of action: depleting, killing, agonistic, antagonistic
- Different antibody isotype formats: +/- immune effector functions, different FcR affinities
- Growing number of cancer types
- Multiple pharma and biotech players
- Multiple combinations
- ……*and more to come!*

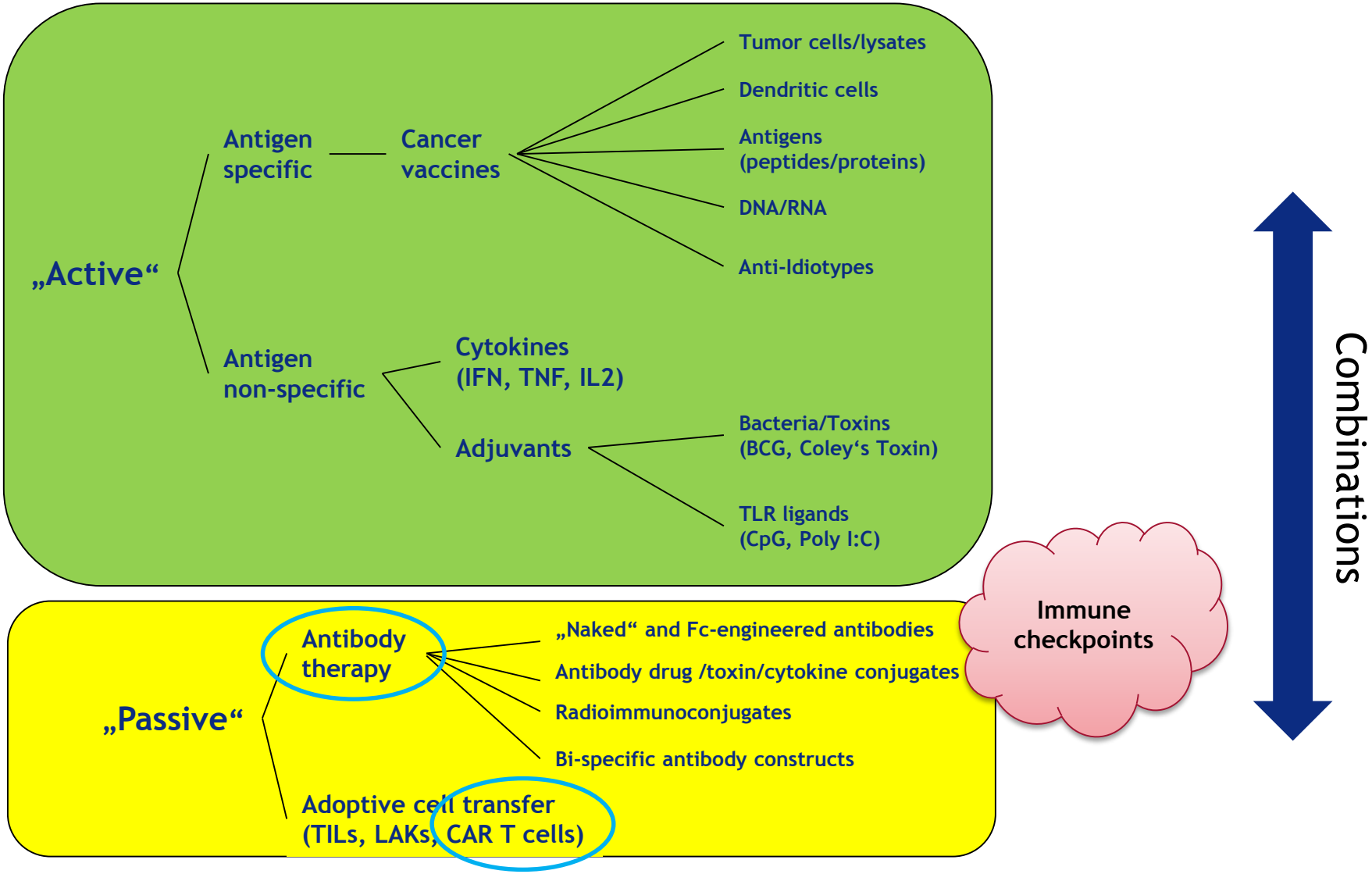
Cross Tumor Potential Shown with PD-1/PD-L1 Agents



Source: Lawrence et al., Nature 2013; Leerink Partners LLC

Cancer Immunotherapy

Active vs. Passive Immunization



Combinations as Next Logical Step & More To Come

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- **Many combinations and schedules in testing, including combination of modalities (e.g. chemotherapeutics, vaccines, radiotherapy, other targeted therapies)**
- **Ipilimumab and Nivolumab combined with impressive response rates of**
  - 41% complete (10%) and near complete (31%) response-rate
  - yet comes at a cost of 53% of pts with grade 3 and 4 adverse events

- **Various agents in phase I or lined-up for entry into human:**
  - LAG3, CD70, TIM3, B7-H3, 4-1BB ("classical" T-Cell Immunological Synapse)
  - KIR, NKG, MICA (NK-Cell Immune Modulation)
  - CSF-1R (Modulation/Attenuation of Tumor Promoting Macrophages)
- **Outlook into immune modulation by addressing further cell types**
  - CXCR2 (MDSC suppression – myeloid derived suppressor cells)

Interest by Big Pharma – Recent Deals

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Companies		Deals
Novartis	CoStim	Acquisition: PD1, PD-L1 assets, IP
AstraZeneca	Amplimmune	Acquisition: AMP-224, AMP-514, IP
Merck & Co	Pfizer	MK-3475 (anti-PD1) + PF-05082566 (anti-CD137) phase I combination
Merck & Co	Ablynx	Multitarget collaboration agreement; bi-, trispecifics
BMS	Five Prime	Co-development agreement
BMS	CytomX	Collaboration agreement
Bayer	Compugen	Collaboration/licensing agreement
Pierre Fabre	Aurigene	Licensing agreement: anti-PD-1 peptide
Pfizer	MD Anderson	Research on immuntherapy combinations
J&J	MD Anderson	Research on immuntherapy combinanions
Janssen	BiocerOX	Collaboration agreement
Merck Serono	MorphoSys	Collaboration agreement
Jounce Therapeutics	Third Rock Venture	47 Mill US$ Series A funding

Outlook & Challenges

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- Immune intervention to fight cancer can be successful!
- Immuno-oncology aims to swing the immune system back into action by either „releasing the brakes“ or „pushing on the accelerator“ and requires multiple steps
- Interactions between various immune cells, components of the tumor microenvironment and tumor cells are complex and take place at different sites
- There is no one immune checkpoint but rather a bunch of them
- Major differences between immune systems of rodents, non-human primates and humans result in poor predictivity of non-clinical models
- Immunotherapies targeting checkpoints can take a long time to first clinical response (weeks to months!)
- Checkpoint inhibitors do not necessarily show classical dose-response curves
- Expression of checkpoint inhibitors is dynamic and does not necessarily predict response; biomarkers?
- Approaches need to be adapted to tumor type/immune status of patients (immunoscoring)
- Combination therapies are imminent, however, selection of suitable combination partners, timing & sequence of application and complexity of clinical trial design will be challenging; treatment costs?
- YIN & YANG: Balance between tumor immunity and autoimmunity is delicate, thus side-effect profiles need to be watched carefully

Immuno-Oncology – Aspirations for The Future

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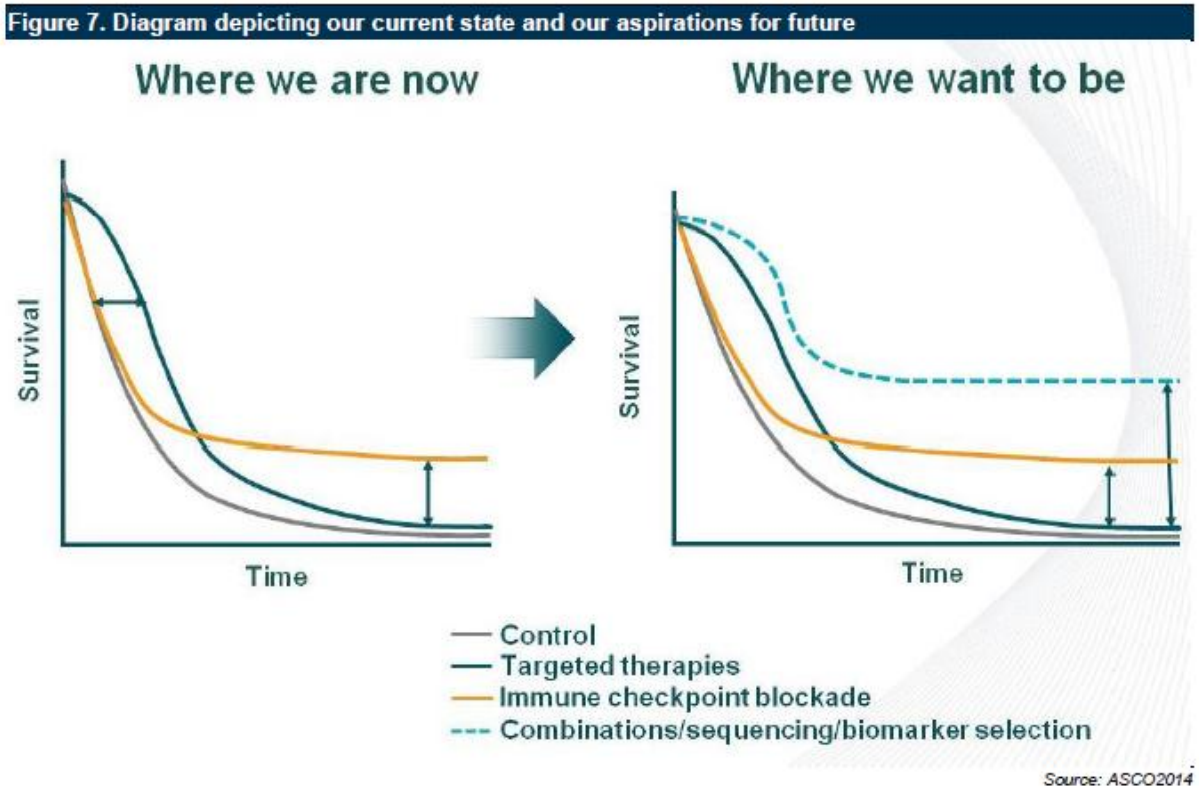
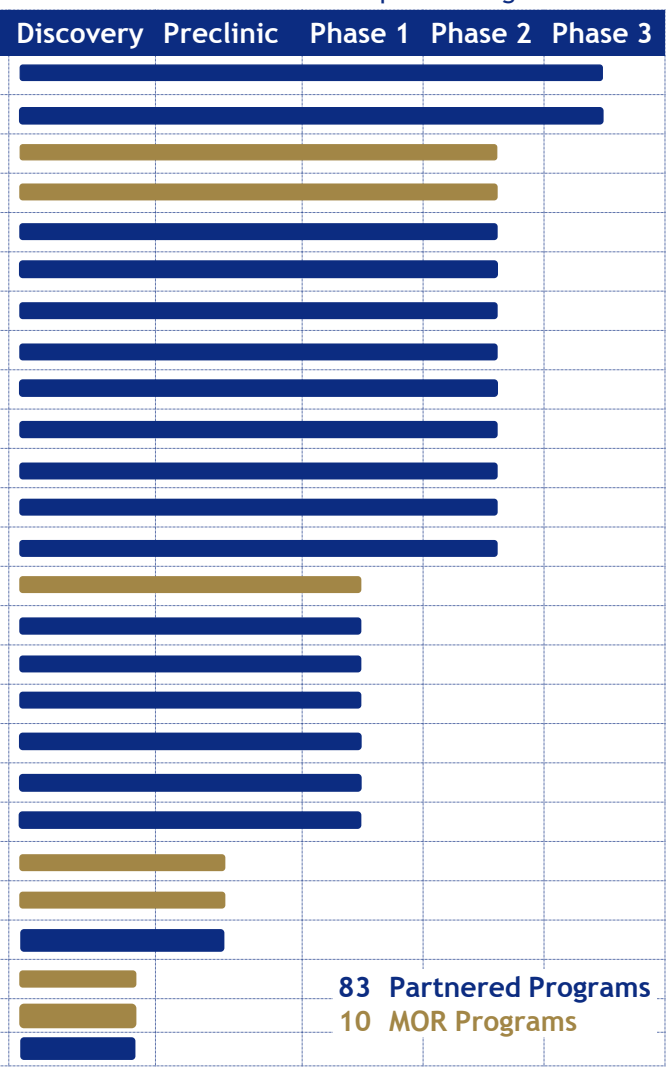


The MorphoSys Pipeline
20 Clinical Programs, 93 Total

Most advanced development stage

Program	Partner	Target	Disease Area
Bimagrumab (BYM338)	Novartis	ActRIIB	Musculoskeletal
Gantenerumab	Roche	Amyloid-ß	CNS
MOR103	GSK	GM-CSF	Inflammation
MOR208	-	CD19	Cancer
BHQ880	Novartis	DKK-1	Cancer
CNTO3157	Janssen	-	Inflammation
CNTO6785	Janssen	-	Inflammation
Guselkumab (CNTO1959)	Janssen	IL23p19	Inflammation
LFG316	Novartis	C5	Ophthalmology
LJM716	Novartis	HER3	Cancer
NOV – 3	Novartis	-	not discl.
Tarextumab (OMP-59R5)	OncoMed	Notch 2	Cancer
VAY736	Novartis	BAFF-R	Inflammation
MOR202	Celgene	CD38	Cancer
BAY94-9343	Bayer	Mesothelin (ADC)	Cancer
BI – 836845	BI	IGF-1	Cancer
NOV – 7	Novartis	-	Ophthalmology
NOV – 8	Novartis	-	Inflammation
PF-05082566	Pfizer	4-1BB	Cancer
Vantictumab (OMP-18R5)	OncoMed	Fzd 7	Cancer
MOR209/ES414	Emergent	PSMA/CD3	Prostate Cancer
MOR106	Galapagos	-	Inflammation
27 programs	Various	-	Various
Immuno-oncology program	Merck Serono	-	Cancer
4 MOR programs	Various	-	Various
39 programs	Various	-	Various



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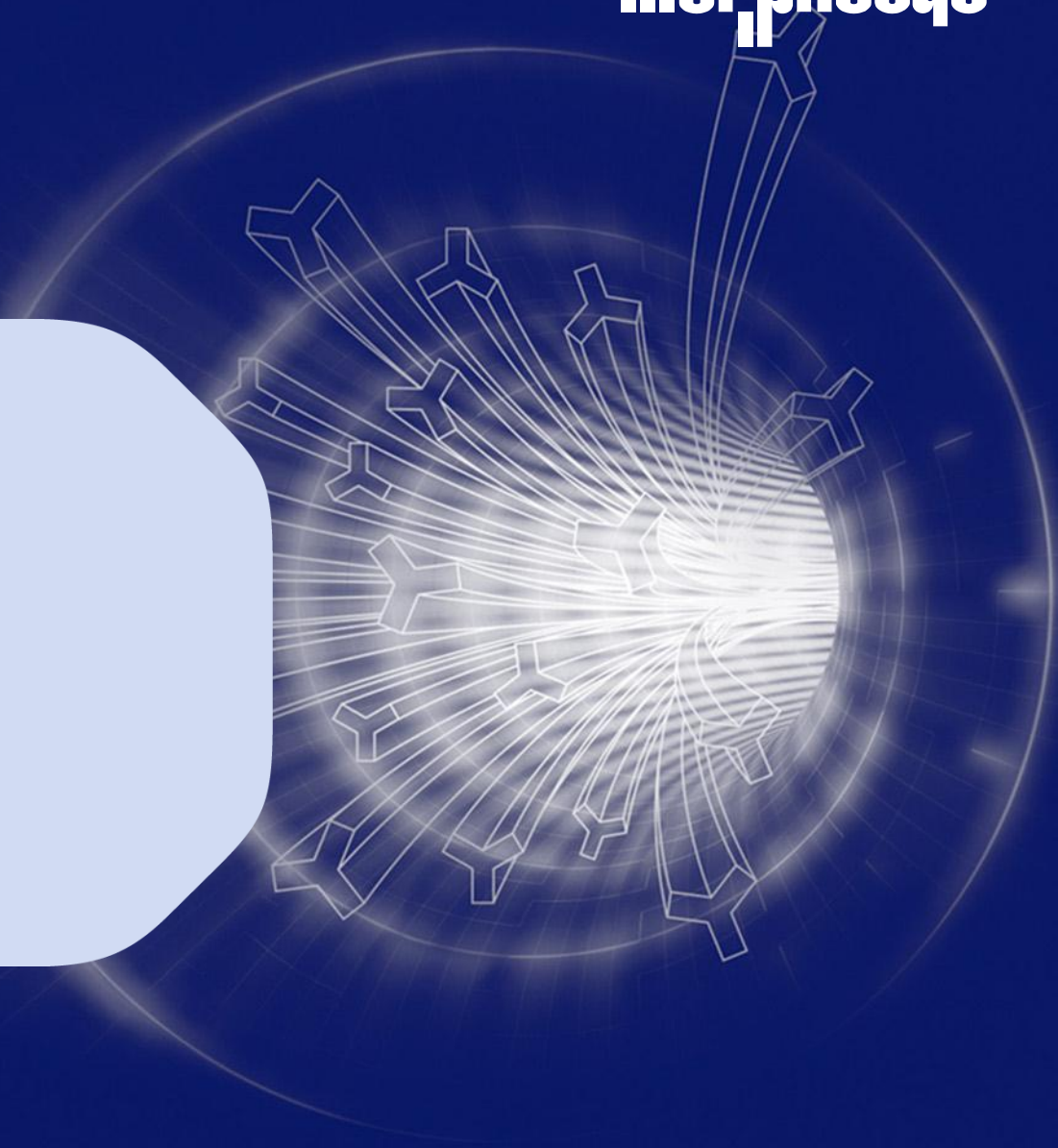

Thank You !

MorphoSys is a Leader in the Discovery & Development of Therapeutic Antibodies

- MorphoSys…
  - Founded 1992
  - Located close to Munich, Germany
  - Listed on the Frankfurt Stock Exchange
  - Around 300 employees
- Most successful antibody library technology in the industry based on number of MorphoSys antibodies in clinical trials
- Proven antibody development expertise
- Highly successful track-record of partnering with pharmaceutical companies world-wide
  - Next generation technologies
  - Proprietary innovative compounds
- Financially strong
  - 2013 profitable with revenues of EUR 78 million
  - Cash position of around EUR 375 million
- Deep pipeline of proprietary and partnered therapeutic programs