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Advances in Cancer Immunology and Immunotherapy

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Abstract- *Background:* Recent next-step advances in cancer immunology are found on many frontiers: on targeting cancer and cancer niches with specific conjugated conjugated or unconjugated monoclonal antibodies, by activating immune responses via monoclonal antibodies, antigens and vaccines, cytokines, costimulatory pathways and checkpoint modulators, or by adoptive cell transfer, comprising the newly approved CAR T biomedicines, and many combinatorial strategies for an increasing amount of sub-indications. The field has quickly carved out a new 50 billion dollar biologics industry that will double again in only 4-5 years. It is a topic of immense economic, societal, political, scientific, healthcare-related, and biomedical interest. Despite this importance, unbiased, more complete and more holistic overviews of these new markets and biomedicines technologies are widely missing.

Methods: Comprehensive listings and a brief market research are used as a basis to systematically summarize all of the approved cancer immune-therapeutics including their prospective sales estimates to structure a more holistic scientific review and in-depth strategy discourse that provides a better understanding from an overview perspective of the recent advances in cancer immunotherapy by revealing both, its progress and bias in a more complete bigger picture including the research itself.

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Results: This review, research, and holistic scientific dossier resolves a better understanding from a more global and also molecular perspective and bears far-reaching economic, R&D, and biomedical implications arising from the recent advances, and it summarizes the progress and bias in cancer immunology and immunotherapy. The ambidextrous balance of explorative and exploitative progress has been biased in academia, the industry, and by the FDA and EMA. Many new blockbusters are selling big while the molecular mechanisms are still not fully explored for the still new and promising biologics innovations, as not enough postdocs were hired.

Conclusion: Today's first-generation next-step cancer immune-therapeutics have only partially solved the histocompatibility defiance retaining refractoriness of cancer: progression-free survival and overall survival have slightly improved but cost-benefit ratios are still relatively low, while SAEs and AEs are still too frequent. Malicious consulting has caused systemic biases and artificial blockades for postdocs in management and R&D which must be reverted. The profits gained from the markets now allow more fair opportunities for senior postdocs to find better molecular, cellular, and mechanistic strategies. This is in line with the view of regulators and legislators and it is now the turn of the industry to act. There is still much potential for new biomedical and business breakthroughs in unbiased cancer research and unbiased cancer immunology.

Keywords: cancer, immunology, immunotherapy, CAR T, antibodies, ADC, CDC, ADP, bias, review, market, advances.

I. Background

In approximately two decades, from 1997 to 2018, the approved medicinal product field of cancer immuno-therapeutics has gained an overwhelming market share and has been a major managerial and biomedical game-changer in the pharmaceutical sector. Simultaneously, all of the related scientific progress has not experienced a somehow comparable breakthrough in cancer immunology as the economic biologics blockbusters might globally indicate. Still, some real progress has been achieved by the first-generation of biologics anti-cancer drugs but more progress is still needed. New unbiased reviews that holistically overview the most recent advances in anti-cancer immune therapies and all of its approved therapeutic drugs were much elusive or incomplete in 2018. Although recent reviews exist, in nearly all cases, they have a different goal or focus, or a sub-focus on the field that doesn't give the big picture as an updating overview with the key questions, which is the objective of this work [1]–[9].

II. Methods

Statistical Pearson's Correlation Coefficient Studies, or PPMCC-Analysis: This widely standardized, utilized and intuitively understood statistical procedure was used to comparably measure the dependency of a linear association between two individual data sets by calculating the individual Pearson's product momentum correlation coefficient for each array of data, x, y, in a two-dimensional correlation setting, and according to the commonly used standard formula:

$$\textbf{Dependence } R_{x,y} = \frac{\sum_{i=1}^{n}(x_i - \bar{x})(y_i - \bar{y})}{\sqrt{\sum_{i=1}^{n}(x_i - \bar{x})}\sqrt{\sum_{i=1}^{n}(y_i - \bar{y})}} \qquad \bar{x} = \frac{1}{n}\sum_{i=1}^{n} x_i \quad \textit{and} \quad \bar{y} = \frac{1}{n}\sum_{i=1}^{n} y_i$$

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III. Advances in Cancer Immuno-Therapeutics in Four Chapters

Cancer has remained a leading cause of death worldwide [10], and immunotherapy is still a newly emerging and promising strategy of molecular biology to fight its mortality rates. The National Cancer Institute defines immunotherapy as a type of cancer treatment that helps the immune system to fight cancer. Cancer immunotherapy includes (I) monoclonal immunotherapy, (II) adoptive cell transfer (ACT), (III) cytokines & co-stimulatory pathways, and (IV) cancer vaccines (Fig. 1), reviewed here in four chapters with all drug listings.

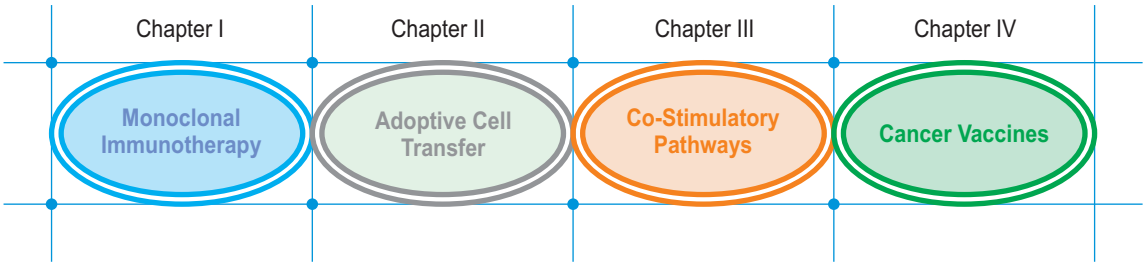

Figure 1: The Four Types of Cancer Immunotherapy in Four Nutshells: Review Chapter I - IV

Conventional cancer treatments are still the most practiced and the most canonical therapies of today`s medical anti-cancer strategies. They comprise surgery, chemotherapy, and radiation therapy, while cancer immunotherapy is still the new approach that is further becoming further becoming increasingly accepted and has only recently been innovated and approved, and since 1997. For two decades of cancer immunology, mainly monoclonal antibodies (mAbs) were developed to treat a few types of cancers, and now, an abundance of cancer indications are co-treated with mAbs and mAbs are increasingly filling the international clinical markets and pipelines. Cancer immunotherapy is still to be viewed as a relatively new biologics strategy and is an ascending new field that grew rapidly very huge due to its opportunities before it was leaving all of its scientific infancies or potential risks. It has also become the next step and new module of combinatorial cancer treatments as mAb cancer therapy is and will be often coupled to regimes like chemotherapy, and by a prevailing trend, they are mainly approved for refractory and reoccurring cancer indications, (i.e. for patients that need) new help and hope from new innovations.

Chapter I

IV. Monoclonal Antibody Immunotherapy

In early 2018, approximately 32 monoclonal antibodies were approved by the FDA or EMA for cancer immunotherapy for a cancer indication and medical purpose (see Table 1). There are more than 10.000 clinical studies linked to these 32 medicinal products of the biologics type, which are registered at the NIH and at the NIH database https://clinicaltrials.gov [11], that give an update on the trials by providing the entire listings for all of them and access to more information, forming the basis of the review.

Today, the global market of cancer therapeutics is already worth ca. $100 billion (bn; US$) and immune-therapeutics have quickly gained 50% of the overall oncology drug market with sales of $54 bn in 2016 and a forecasted market of $100 bn in 2022 that will continue to grow to $118.8 bn in 2025 [12]. 55% of this market in 2022, around $55 bn, are expected by recent sales forecasts of these 32 mAb cancer therapeutics (see Table 1). Another $45 bn will be yielded from even higher sales than today and from newly approved drugs including mAbs (chapter 1 and partially 3), but also CAR T (chapter 2) and cancer vaccines (chapter 4). In the next decade, there will be immune-therapeutics available for up to 60% of all cancers [12]. The top-5 best-selling cancer drugs [13] and their sales forecast for 2022 reflects this development [12], shown in Table 1: 3 out of 5 top-selling cancer drugs are mAbs: i.e., Opdivio, Imbruvica, and Keytruda, which are expected to make $27,5 bn in 2022 [13] and they include or will include several additional indications.

Cancer immuno-therapeutics, however, can often seem comparably fast in their development (Table 1, 2). For instance, after only 20 years, they predominate in the cancer market in sales [12], [13]. But the low number of targets and the high number of clinical studies per medicinal product are also telling another and a quite different medical story, and one could already derive potential R&D bottlenecks: (i) to few basic and preclinical research of targets, mechanisms, and diversity of biologics (ii) lack of sustainable careers for researchers and systemic global blockade of senior postdoctoral experts, (iii) research and market barriers, rising R&D expenses, lack of R&D understanding in the hierarchy, expenses, lack of transparency, lack of eligibility and access, false strategies and some stereotypic management that bypasses the postdoc jobs in the pharma industry, and (iv) a consultancy-conspiracy organized crime network that illegally sabotages the postdoc job market. Postdoctoral

competency is the key to unfold the power of cancer immunology in cancer research, clinical trials, and management, but they are systematically blockaded world-wide as consultancies seem to fight the intelligent workforce globally. The big next steps in cancer immunology are too difficult for others and can only be achieved if postdocs get the career chances they need.

Table 1: Top 5 Selling Cancer Drugs [13]. Table adapted from Taylor P, FiercePharma 2017

#	Drug Brand	Generic Name, INN	Firm Name	Sales 2015	Sales 2022	Costs/ patient	Drug Type	Some Major Approved Cancer Indications
1	Revlimid	Lenalidomide	Celgene	5,8 bn $	13,44 bn $	163 T$/a	Chem	Multiple myeloma, MantleCell Lymphoma
2	Opdivo	Nivolumab	BMS, Ono,	1,12 bn $	12,62 bn $	103 T$	mAB	NSCLC, metastatic melanoma, RCC, HL
3	Imbruvica	Ibrutinib	AbbVie	1,23 bn $	8,29$ bn $	127 T$	mAB	CLL, MCL, Waldenström macroglobulinemia
4	Keytruda	Pembrolizumab	Merck & Co	0,56 bn $	6,56$ bn $	150 T$	mAB	Adv. Melanoma, NSCLC, head and neck SCC
5	Ibrance	palbociclib	Pfizer	0,72 bn $	6,01$ bn $	100 T$	Chem	Metastatic Breast Cancer

As a result, drug discovery of the last two decades in immune-oncology has also been coined by a lot of uncertainty that was covered by conspiracy-biased strategic advisory networks that mainly aim to fool the investors and firm owners - not only HR and hiring staff with false hiring procedures and stereotypes against postdocs. For instance, a crime-like CV-keyword system that builds on experience that only crime-network-members are allowed to get or make. Postdocs need a starting position in the industry and their experience is always more relevant and fully transferable also from field to field and profession to profession. HR intentionally sabotages them to steal all jobs from the educated and intelligent and competitive workforce, also in most cancer immunology vacancies, almost always false by default. This drives costs and destroys future achievements everywhere, especially in cancer immunology and biopharma. Every medicinal monoclonal product represents a big investment to firms, and to reduce the investment risks, the behavior of the pharmaceutical sector can be - at least from some perspectives - best described as "resembling the economic sucess routes and targets" and examples are PD-L1, EGFR or CD20 (Table 1 and 2). This has pros and cons, and mainly the cons are the problem. Once a clinical trial had indicated a big potential for commercialization, all further trials were seemingly expanded. This could be described as a rather defensive strategy of biopharma, which again has both, upsides and downsides. The second must be of more interest, as the first is not a big issue: Defensive strategies quantitatively deal with many cancers but can qualitatively fall short for novelties, which is termed “hyper-exploitation bias”. Innovation today is globally biased.

As a result, more drugs are likely to fail in trials than in the 70`s – and there could be even less biomedical breakthrough – despite all and despite most defensive measures maybe since the emergence of the drug discovery field, because a better ambidextrous balance between exploration and exploitation is needed [15], [16]. More brave and smart exploration of the mechanism is still needed like independent R&D opportunities for postdocs that starts with ending the massive discrimination of experienced postdocs on the job market. Blockading postdocs has become a bad trojan horse back-office strategy goal of the conspiring consultancy networks. Intrapreneurs and managing and researching postdocs are increasingly needed [17], more than before, also in cancer immuno-therapeutics.

For a diversified R&D portfolio, there might be too many defensive strategies and a focus on too reductionist molecular models, and concerns about the predictive validity of the stock of academically and industrial screening models that have emerged [14]. Intrapreneur postdocs [17] can best solve such issues.

Still, biopharma has achieved a big economic sales success in the last 20 years in the field of mAb-therapeutics with unconjugated or toxin- or isotope - conjugated mAbs for 16 cancer targets (Table 2).

While investing in cancer immunotherapeutics can be seen as a vital sign of a ‘pro-active’ and innovative industry that follows the economic breakthrough of Rituxan and Herceptin that were approved by the FDA in 1997 and 1998, respectively (see Table 2: approved monoclonal antibody development in chronological order), the choice of targets and biomedical strategies may can be viewed as ‘a less diversified and reductionist portfolio strategy or as sales-protective and with a focus on risk minimization. Most big pharmaceutical companies also needed to have “some iron in the fire” and thus focused on similar targets – a two-sided sword that leads to some bias, also in the incentive game that is made by

the regulators, i.e., FDA and EMA, one could asume, but also a big step forward into biologics. A closer look at the molecular mechanisms of the 16 targets can even shed some more light on the recent and prevaiing thinking in bioharma industries and mAb investigational medicinal products to treat diverse human cancers (Table 2). Next to the big success of mAbs, one can scientifically ask: how much is the market biased and how well is the entire field doing, how can we assure its future progress?

Table 2: Approved Monoclonal Antibodies for Cancer Therapy

Drug Brand	INN	Corporation	Target	mAb	FDA	EMA	Cells	Indications	Peak Sales	Trials 2018
Rituxan®	Rituximab	Roche/Genentech, Biogen Idec	CD20	chimeric IgG1	1997	1998	CHO	CLL NON-HL, B-cell leukemias	2,29 bn by 2022	1875
Herceptin®	Trastuzumab	Roche, Genentech	EGF: HER2	humanized IgG1	1998	2000	CHO	HER-2 positive Breast Cancer	2,5 bn by 2023	900
Mylotarg®	Gemtuzumab ozogamicin	Wyeth, Pfizer; CellTech/UCB	CD33	humanized IgG4	2000	2018?	NSO	AML	0,35 bn by 2022	76
Campath®	Alemtuzumab	Millenium Ph, Genzyme	CD52	humanized r-IgG1	2001	2001	CHO	CLL, CTCL, TCL	1,25 bn 2020	340
Zevalin®	Ibritumomab-tiuxetan	Biogen Idec	CD20	mouse IgG1	2002	2004	CHO	CLL NON-HL Non-Hodgkin L.	0,12 bn by 2020	98
Bexxar®	Tositumomab /+I-131	GSK, Corixa	CD20	mouse IgG2a	2003	2003	Hybri doma	CLL NON-HL, follicular lymph.	discontinued	155
Avastin®	Bevacizumab	Roche/Genentech	VEGF	humanized IgG1	2004	2005	CHO	lung, renal, CRC brain, breast c.	2,7 bn by 2023	2246
Erbitux®	Cetuximab	Bristol-Myers Sq., Merck KGaA	EGFR	human IgG1	2004	2004	Sp2/0	CRCs, head, neck, cancers	1,7 bn by 2023	818
Proxinium®	Proxinium	Eleven Biotherapeutics	EpCAM	humanized fusion	2005	2005	CHO	Sq. Cell Carcin. of Head Neck	0,4 bn by 2020	5
Vectibix®	Panitumumab, ABX-EGF	Amgen, Abgenix Inc.	EGFR	human IgG2	2006	2007	CHO	CRCs, diverse cancers	0,67 bn by 2023	225
Removab®	Catumaxomab	Fresenius BT, Trion P./NeoP.	CD3, EpCAM, Fc	chimeric IgG2	N/A	2009	CHO	malign. ascites in metastatic c.	0,25 bn by 2022	16
Arzerra®	Ofatumumab	Novartis, Genmab	CD20	human IgG1	2009	2010	CHO	refractory CLL	0,25 bn by 2022	117
Adcetris®	Brentuximab	Seattle Genetics	CD30	ADC IgG1 fusion	2011	2012	CHO	ALCL, HL Hodgkin L.	0,4 bn by 2022	122
Yervoy®	Ipilimumab	UC-Berkey, Medarex, B.M.S.	CTLA-4	human IgG1	2011	2011	CHO	Melanoma, NSCLC, cancers	2,3 bn by 2020	439
Xgeva® Prolia®	Denosumab	Amgen, Micromet Inc.	RANK:RANKL	human IgG2	2011	2011	CHO	Prostate, bone, div. cancers	1,1 bn by 2023	158
Perjeta®	Pertuzumab, 2C4	Roche, Genentech	HER: HER2	humanized IgG1	2012	2013	CHO	HER-2 positive Breast Cancer	4,7 bn by 2022	143
Kadcyla®	Trastuzumab-emtansine	Roche, Genentech	T-DM1-HER2	humanized IgG1	2013	2013	CHO	HER-2 positive Breast Cancer	2,5 bn by 2020	78
Gazyva/ro®	Obinutuzumab, GA101	Roche, Glycart Biotech AG	CD20	humanized IgG1	2013	2014	CHO	CLL, follicular lymphoma	1,5 bn by 2023	115
Blincyto®	Blinatumomab	Amgen, Micromet Inc.	CD19/CD3 engager	mouse BiTEs	2014	2015	CHO	Philadelphia Chr. Neg. ALL	0,2 bn by 2023	43
Keytruda®	Pembrolizumab	Merck & Co	PD-1	human IgG4/κ	2014	2015	CHO	Melanoma, NSCLC, cancers	10,2 bn by 2022	700
Cyramza	Ramucirumab	Eli Lilly, Im-Clone Systems	VEGFR2	human IgG1	2014	2014	NSO	Solid tumors, NSCLC, cancers	1,5 bn by 2023	81
Sylvant®	Siltuximab	Janssen Cilag	IL-6	chimeric IgG1/κ	2014	2014	CHO	Neoplastic Cancers; other	1,0 bn by 2023	24
Darzalex®	Daratumumab	Janssen Cilag	CD38	human IgG1/κ	2015	2016	CHO	Multiple Myeloma	4,2 bn by 2022	78
Emplicity	Elotuzumab	Bristol-Myers Squibb	SLAMF7	human IgG1	2015	2016	NSO	Multiple Myeloma	4,2 bn by 2022	46
Portrazza	Necitumumab	Eli Lilly	EGFR	human IgG1	2015	2016	NSO	NSCLC, diverse carcinomas	0,4 bn by 2022	19
Opdivo	Nivolumab	Bristol-Myers Squibb	PD-1	human IgG4	2015	2015	CHO	NSCLC, diverse cancers	1,7 bn by 2022	591
Unituxin	Dinutuximab	United Thera-peutics Europe	GD2	human IgG1/κ	2015	2015	Sp2/0	Neuroblastoma	0,1 bn by 2020	24
Lartruvo	Olaratumab	Eli Lilly	PDGFRα	human IgG1	2016	2016	CHO	Solid Tumors, STS	0,41 bn by 2020	19
Tecentriq®	Atezolizumab	Roche, Genentech	PD-L1	human IgG1	2016	2017	CHO	NSCLC, diverse cancers	2,0 bn by 2022	218
Bavencio®	Avelumab	EMD Serono, Merck; Pfizer	PD-L1	human IgG1/κ	2017	2017	CHO	NSCLC, Solid Tumors, diverse	2,2 bn by 2022	98
Imfinzi®	Durvalumab	AstraZeneca UK	PD-L1	human IgG1/κ	2017	2017	CHO	NSCLC Lung and solid tumors	2,2 bn by 2022	221
MVASI first biosimilar	Bevacizumab; similar to Avastin	Amgen, Allergan	VEGF	humanized IgG1	2017	2018	CHO	lung, renal, CRC brain, breast c.	0.8 bn by 2023	Similar to2246

Most researchers in the field have shied away from trying to give an official answer, as there are simply too many clinical trials (10.088 in 2018) and every trial is designed differently, is often partially standardized, and is often entirely using the same settings, different patient population or cohort with different demographics and patient features, different treatment regimes, different demarcations, different pretreatments, different objective response measures, outlooks, different refractory or relapsed cancers, first- or second-line treatments, combinatorial strategies, in different locations, with different read-outs and concentrations that all hampers can complicate to give an overview for all stakeholders. Additionally, less than 50% of clinical trials have not been published so far and all the data is mainly not available [18].

Consequentially, when we think about cancer immune therapeutics or 'immunotherapeutics', there is a common and widespread lack of discussion and knowledge about the overall big picture of this novel targeted cancer therapy approach. To gain a better understanding of the overall developments, one must first list all biologics to gain an overview that helps to see and to understand the big trends (see Table 1, 2). The economic crevasse has happened with the 'first approved' mAb of Genentech in 1997, which is now a part of ROCHE, and ca. 31 mAbs that were following. This might have been the cause of a progress bias in our business incentive system, and a bias in our scientific understanding about some of the key biomedical estimates. Biologics for cancer treatment clearly bear new value but can also be viewed from the health care provider and insurer perspective, and updated by an independent science perspective, as they continue to place a significant economic burden on the healthcare system and its stakeholders, and do not extend life for decades but still only many months on average. As a result, new affordable biosimilars like MVASI are now already emerging, despite of the foreseeable and present lack of precise regulations for biosimilars since decades (Table 2). A key question is how to best define identical or similarity for biologics, to not always have to start full clinical trials a new, or and how similar is identical and which read-out is finally securing this? In almost 20 years of cancer biologics, they took over 50% of all cancer drug expenditure, and one could find an economic bias in the incentive system if one would look at benefit-to-risk ratios. Still, this incentive drove the field into developing new first-step routes of treatment, but incentives and opportunities might be missing to achieve the next steps of a higher efficacy with less frequent and serious adverse events. For instance, today, a drug that saves 20 years of patient's life would earn as much as a drug that saves 10 months, or even less. This might be on the one side a typical product lifecycle question but on the other side, it is also a breakthrough innovation issue that is not finally resolved in the sector. Firms must have incentives to innovate but innovators in firms too (17): The hiring of postdocs and diversified biomedical R&D strategy portfolios are the main solution to extend the protfolios (Table 2).

Pharma-2.0 has much remained in an ongoing transition to Pharma-3.0 while they already digitalize for Pharma-4.0 and consultancies have prematurely started to advise a Pharma-5.0 irrespective of the quality and progress of all decimal places on this way. Biologics medicines can be complex but now they first went simple and the first big steps to take were assisted by the FDA and EMA that wanted to help in the transition by allowing lower bound efficacy in new class biologics drugs, especially in the cancer therapeutics field that did not see much progress since many years at that time. Hence, mainly mainstream mAb irons were put into the fire (Table 2). The sum of all clinical trials indicates that some progress has been achieved (table 2). But the cost-effectiveness for innovation, healthcare economics, and efficacy are not clearly a comparable breakthrough in light of the outstanding$55 bn sales breakthrough, all expectations growing globally [12]. They can be seen as the first-generation drugs that should enable a second-generation. The billion-dollar sales would especially make much sense if these funds are reinvested into theoretical and practical R&D and innovation. This means, hire postdocs and give them a research or managerial chance - to lead the way.

Achieving what the experts have shied away from, Figure 2 gives an overview of some key stats and facts of mAb-cancer-therapeutics by integrating all rough estimates and trends in clinical trials. This yields a simplified representation and uncovers the bigger picture (Fig. 2): The objective and overall response rate (ORR) is on average not much higher than 30%, while serious adverse events, while serious adverse events (SAEs) and adverse events (AEs) for mAb-cancer-therapeutics have still remained relatively high (SAE and AE demarcations are blurred and standardizations are unclear) for all mAbs on average ca. 60% (Fig. 2): an estimate only, as the total number of patients with "any type of AE" is missing by default as an official summary or in the label. Only in comparison to radiation or chemotherapy, one would tolerate such adverse events. mAb-cancer drugs are often given in a combination with chemotherapy thereby significantly increasing the risk of SAEs and AEs and many further complications, and new incentives are elusive. The FDA or EMA officially build their decision on benefit/risk-assessment of efficacy to adverse events and also costs, while the later, is a more managerial or political decision of regulators. The benefits are found in the efficacy of the drugs that are also summarized in Figure 2B: The measured duration of response (DOR) is still short, i.e., less than 10 months on average for on average only 30% of respondents, while progression-free survival (PFS) is still below 10

months, complete responses can be found around 10 months, while the majority are only partial responses that are not a stable health solution to cure progressing cancers (Fig. 2). Some mAbs are better but there is more research work to be done - and the transferable skills of postdocs are the key to the solution.

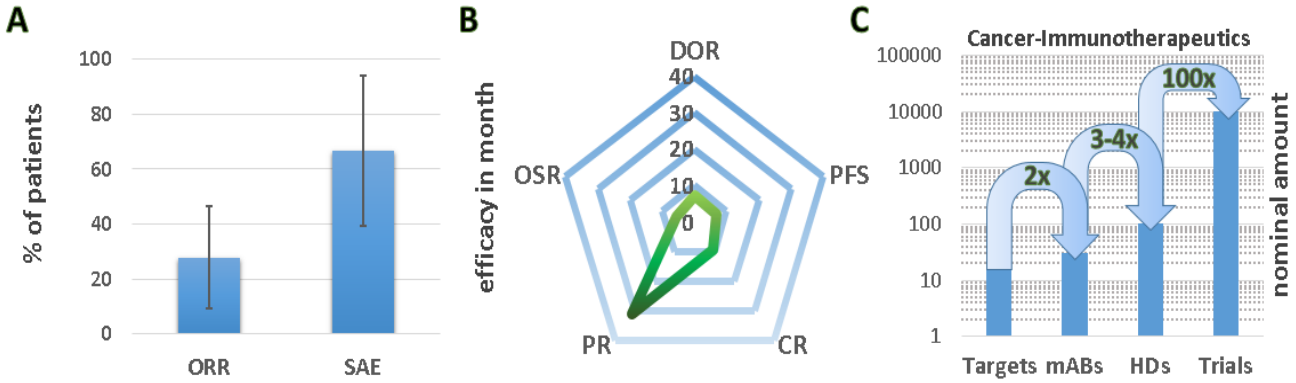

Figure 2: Cancer Immunotherapeutics, overall statistics of simplified rough estimates of clinical trials; ORR: Objective Response Rate (also: Overall Response Rate), SAE: Serious Adverse Events; DOR: Duration of Response (this is the duration of the ORR), PFS: Progression-Free Survival, CR: Complete Response, PR: Partial Response, OSR: Overall Survival Rate; rough estimates of representative studies to reveal the general trend of all 10.088 trials. A normalization is not possible due to a lack of standardization, only rough estimates, no liability assumed.

New efficacies could be achieved in very difficult fields of oncology, however, even better mAb drugs are still needed (Fig. 2). They have remained elusive although they are possible now - more than ever before - but this will require to supply postdocs with chances and more jobs to find the combinations and ways. One should view this new overall result as a big picture of the first-generation of biologics, better has yet to come that must prolong survival for decades. Let postdocs find the mechanisms, "both autoimmunity and cancer could be theoretically healed at once by hiring most postdocs". Also, patients want and have to be completely cured and not only partially: the CR and OS must still get much better. While the technological know-how in GLP, GCP, GMP, and the production pipelines and clinical trial pathways are now established for big pharmaceutical companies, the quality-related future economic incentives for continuous improvement of the markets and biomedicines might be falling a bit, like in all markets of today. But there is still a very big jackpot waiting for whoever solves the billion-dollar questions of how to eradicate cancers with cells that can escape immune control with immune-theraputics while not so much attacking the host tissus and cells. The economic incentive issue can be maybe compared to the automotive industry: the transition from Otto engine to electronic or other engines could be potentially delayed: "a predictable delay of next-generation innovation" in mainly oligopoly-some markets. But the 1st-generation is not that old, it is still young, and it is still too early to say. But like the automotive industry, pharma could be not highly interested to replace a recently established profitable business model. Only a fair competition for the best cancer solution is constructive: i.e., more postdoc jobs and more intelligent filters for clinical trials: less money and more science related trials. 6 targets, 31 mAbs (2x targets), ~100 indications of human diseases (HDs, 3-4x targets) and 10.088 clinical trials (100x targets) reveal a striking lack of diversity: a bottleneck in the R&D pipeline that can be still further improved (Fig. 2C). What if low efficacies are a non-specific Klein-Boon effect within the noise or variation of single trials [19]? It should be tested uniformly in all trials not in just one to find out and also due to the need of fair competition. [19]? No Often control mAbs are missing, which causes statistical instability of trials. Unlikely but worth thinking and testing one day one may suggest just as a footnote-like comment.

Clinical trials and cancer therapeutics is often nothing for medium-sized firms or businesses, it is a métier of too-big-to-fail pharmaceutical giants and juggernauts that became very important for the functioning of this sector, even for the economy and the entire healthcare and pharma-system. Many red biotech firms have been established recently but competition is limited due to clinical trial costs. Also, M&As dominate the field, as most of the smaller firms that first developed key mAbs were quickly bought and are usually less innovative after the M&A due to the malicious side effects of M&A advisory and blockages of postdoc intrapreneurs [17] that both stems from a false consultancy advice. The costs, time, and investment horizons are also often just too risky and financially unaffordable for small and medium-sized enterprises, and even for bigger and huge firms. Still, small firms show more breakthrough potential because they are less defensive but outsourcing can be fake and only seems to generate independent agiler satellites at the very first glance. The defensiveness in the new field has led to only 16 targets and 10.088 trials (Fig. 2C). Mainly

additional cancer indications are tested to extend the FDA and EMA approvals to further cancer types. Consequentially, experts have estimated that this might lead to an increase of 10-20% in the amount of covered cancer indications, i.e. cancer types, and could drive 10-30% in sales by means of exploitation of market innovation. But one could economically also argue that it can be worth to also look for additional and better targets and mechanisms instead of mainly expanding on indications. It could also make sense to explore new drugs that more strikingly increase PFS, CR, OS, ORR, patient health, and lifespan (Fig. 2) while reducing adverse effects and mortality. For this, a better understanding of the therapeutic mechanisms of mAbs could be essential and can be gained (Fig. 3) via better research by making more postdocs PIs, managers, and innovators. The repression of postdoctoral life scientists in the age of life science has slowed deep innovation in cancer immunology and in all other fields. Only the rise of the postdoc can revert this strategic consulting mistake that wanted to eliminate the better candidates everywhere, namely postdocs CV experience is used to steal all jobs - as postdocs are hindered to make it - and "cancer immunology" is a keyword like management.

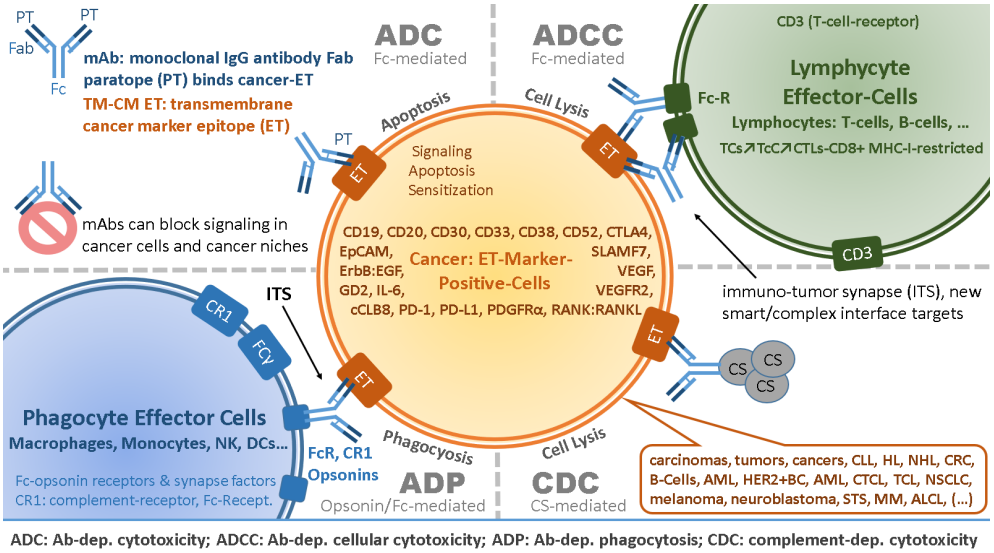

Figure 3: Biomedical Strategies and Therapeutic Mechanisms of mAbs in Immuno-Oncology

The molecular mechanisms of mAb anti-cancer drugs (Fig. 3) can be subdivided into ADC, ADCC, ADP, and CDC. ADC is the abbreviation of mAb-dependent cytotoxicity, ADCC stands for mAb-dependent cellular cytotoxicity, while ADP stands for mAb-dependent phagocytosis, and CDC abbreviates complement-dependent cytotoxicity. The overall effect of these four mechanisms of action of mAb-immunotherapyis of mAB immunotherapeutics is schematically summarized and illustrated in Figure 3 to give the big picture and a general overview. Of note, one can systematically subdivide into the two effector cells, namely phagocytes (blue) and lymphocytes (green), and in protein factors, namely complement and antibody elicited cancer cell toxicity. 3). Also, cancer marker and engager protein targets on effector cells are indicated for the recent mAb-therapeutics in Figure 3. Also, the immuno-tumor-synapse, ITS, now emerges as a new interface with key molecular mechanisms of interest for targeted strategies. To diversify your R&D portfolio you might want to know what works best for these four mechanisms, as this could help you to derive a more diversified and promising portfolio of R&D projects. These belong to senior postdocs to screen for breakthrough medications in an R&D-chance achieving way without junior or senior discrimination. Further biomedical biologics strategies are needed to better the efficacies (see Figure 2B and Table 3). Therefore, a diversified and promising research roadmap is needed.

A correlation of the 31 mAb-cases would slightly suggest that CDC/ADCC/ADP works best for PFS, while ADC alone could be slightly behind, generally speaking, not for an individual mAb per se. Because the signal-to-noise could be a problem of simplified statistical scoring models, and for the Pearson correlation, the scoring contrast was amplified at x2, x3, x4, and x5 (Figure 4). However, this can be shown to make no big difference, as it still basically reveals the same trend towards PFS and involvement of CDC, ORD and involvement of ADP, and ORR that depends on ADP. Although weak, non-stratified correlations are often weak, they can potentially give a new hint: It seems that CDC and ADP are slightly the more promising mechanisms for PFS/ORR/ORD, which could be important for the second generation of mAb cancer drugs. This is unexpected, as the most prominent mechanisms are ADCC and ADC, as believed by cancer scientists, the FDA lables and big parts of the scientific literature. Furthermore, ADCC and ADC is also officially the most chosen strategy of the 31 antibodies in Table 2.

However, if these simplified trends and the weak correlation in figure 4 are true and meaningful (one cannot expect a strong correlation under the heterogeneous settings of conjugated and unconjugated mAbs, then another new big picture emerges that mAbs are working best if they also activate CDC and ADC. This would indicate that mAbs which fully resemble all four natural pathways could work better. Thus, not every new strategy but some could try to even better resemble human mAb-mechanisms. Maybe it is possible to produce better-conjugated mAb in a way that does not interfere with ADP/CDC. The efficacy of mAb cancer treatment has also been suggested to correlate with typical Fc-γ receptor engagement of phagocyte effector cells [20] and functional Fc-receptors are required for ADP and CDC. Thus, it is feasible and would make much sense and could be leading the way to use bionic mAb in intelligent combinations - by hiring more postdocs.

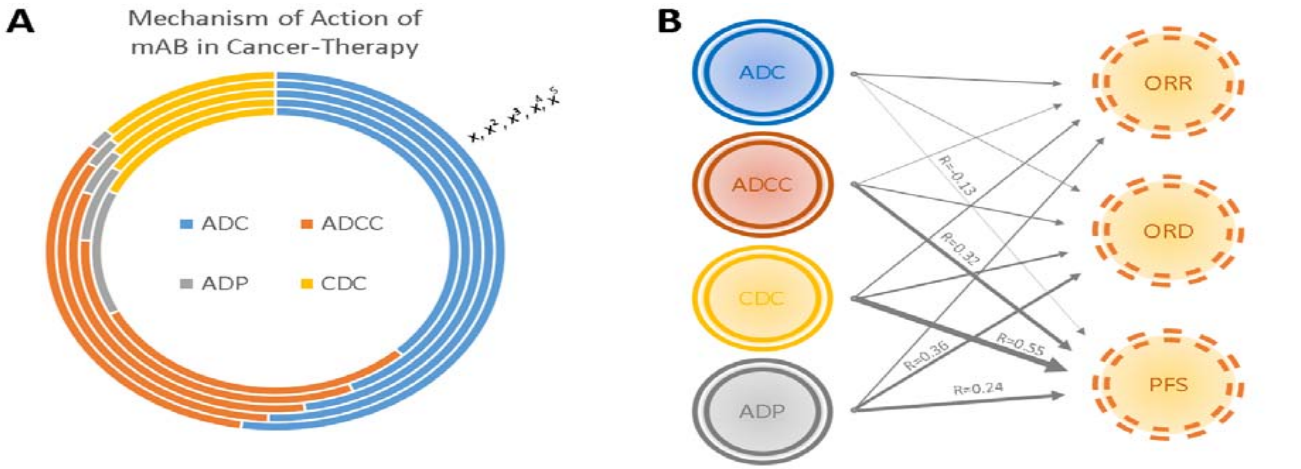

Figure 4: The bigger picture of the mechanisms of mAb cancer immunotherapy. (A) The relative share of mAb mechanisms in the approved cancer therapeutics. (B) Visualization of non-stratified Pearson correlations of ORR, ORD, PFS in its dependency to ADC, ADCC, CDC, and ADP. CDC drives PFS and all mechanisms synergize.

It seems that all mAb-strategies are still hampered by mechanistic barriers of immune cells that do not want to target own tissue, incentive barriers to increase efficacy and reduce adverse events, and HR hiring barriers that do not want to hire enough postdocs who could help to optimize all of these issues. Scientific estimates suggest that many of the adverse reactions could be theoretically converted into a higher efficacy, as the immune system is naturally designed to adapt to more targeted reactions. How to only mark cancer for full eradication remains the question. While the field has moved a step forward, more breakthrough research incentive is needed and more life science postdocs should get real chances in the big pharma hierarchies.

The high amount of AEs and SAEs and reactions stem from several types of immuno-toxicity of mAbs [21]. Most mAbs not only target the tumor but also the host tissue and activate the immune system in unspecific ectopic ways, which can also cause immune side effects that lead to adverse reactions and SAEs. Both could be theoretically optimized by postdocs that are given full PI competency and repsonsibility for better converting AE into efficacy. Funds must be used not for a CV keyword or stage but for a real, brave, promising, and true goal innovation. Traditionally viewed, antibodies are the centerpiece of the so-called “adaptive immune system”. But today, we know that they also play a role for the “innate immune response”, e.g., by mechanistic means of opsonines that can make use of mAbs to tune up the innate immune response in ADP (Figure 2). Generally, the immune system is a highly interactive and widely researched immune cell-machinery that can also integrate adaptive responses between both (i) phagocyte and (ii) lymphocyte effector cells (Fig. 3) and even more cells. This intricate mechanistic ‘immunologics mechanism’ and its ITS interfaces might not be fully understood by today and synthetic mAbs might not fully recapitulate all ‘immunologics’ in the post-IV-administration phase.

Like this “bias in the mechanisms”, the “clinical trial focus bias”, the “mAb-strategy bias”, the “mAb-safety-bias”, also the immunotoxicity assessment could be methodologically biased, which consist of (a) immuno-stimulation (e.g., acute reactions, auto-immune disease, allergic reactions, inhibition of CYP450-dependent signaling and metabolic pathways, some organ- or tissue-specific Ab complications like eyes and skin or brain), (b) immunosuppression (e.g., infectious complications, virus-induced neoplasias), (c) hypersensitivity (e.g., anaphylaxis; immune-complex mediated reactions), (d) autoimmunity (systemic and organ autoimmune reactions) [22] and more. There are many possibilities of its non-clinical and later clinical testing (see FDA, EMA, ICH S6 guideline) [22] to avoid

"method bias" but the safety burdens are not so high in cancer therapeutics like in other clinical trials due to the highest paramountcy of medical help for the terminally ill. Further complications of mAb-therapeutics are to be expected in the future like the dangerous cytokine release syndrome (CRS) that happened for instance in 2006 (TGN1412, a CD28-mAb), later called "cytokine storms" [23]. Especially age-related conditions could increase the risk of cytokine storms, like adiposity that can increase such lethal CRS-SEAs [24].

This has big implications for management and science, as the risk of clinical trial, failure e.g., due to a lethal cytokine storm [23], [24] is significant and became more relevant. The risk of CRS can be reduced by a better understanding of synthetic biology and the molecular mechanisms, i.e. via more research jobs for postdocs. This would improve patient safety and a cost- and risk-reduction of all investments into clinical trials. SAEs can happen due to several reasons, e.g., non-physiological concentration of mAbs and maybe by the unpreparedness of the immune system for this artificial antibody directed towards a body-own target at the high therapeutic dosages (up to ca. 0.1% of the body's antibodies, variable). The more postdocs in research, the better the mechanism are understood, the lower the needed dosages, the lower the SAEs, and the higher the efficacy, the fewer the trial failures, the better the human resource workforce, the better the decisions, and the lower the real cost per drug, is the suggested drug discovery pipeline optimization thinking and working model: let postdocs do their innovative job. Additionally, a closer look into the number of publications, see Figure 4, reveals that more and more adverse events and SAE and reactions are described for the prevailing monoclonal antibody therapeutics, while the publication interest in mAb and cancer is still slightly increasing, also in relation, if compared to the sum of all mAb publications: in summary, the issue of SAE of mAb such as cytokine storms is still not resolved [23], [24], and the FDA drug labels mention SAEs in some more detail.

Most or all mAbs are used in combination with chemotherapeutics, many for relapsed or refractory cancers, and the term chemotherapeutic monoclonal antibody was coined. Both chemotherapy and mAbs can have dramatic serious adverse reactions and it is of utmost importance to further milden them, to convert all serious adverse reactions into an improved efficacy, which should be possible for mAbs-strategies in theory.

Despite the economic waves, the 50-100-bn Dollar-question still remains very much the same: how to better unleash the still hidden power of all mAbs-strategies, or how to best enable and direct the immune system to fight cancer in specific and fully effective ways, how to convert SAEs in efficacy? On average only less than 30% of cancer patients will live 10 months longer, and most will have adverse reactions including SAE. There is enough room for improvement to give postdocs some fair chances. There are several ways to better unleash the real hidden potential of immune-therapeutics in the mAb-field: for example, one could innovate better drugs by engineering the Fc-fragment to improve clinical outcomes. mAb-Fc-engineering can improve parameters like serum-half-life, biochemical interaction and stability, covalent and non-covalent trimming for physicochemical stability and interactions, the role of PTM (post-translational modifications) on the Fc-, VL/H- and CHL/H1-3-regions, such as glycosylation [25]. The correlation in Figure 4 has revealed that the complement system (CSC) and phagocytosis (ADP) can contribute higher efficacies, which could be done via Fc-engineering [25].

The immune system is known for its highly selective and adaptive attacks against pathogens with minimal adverse effects like fever. To unfold the power of mAb it might be important to activate all four modes (CSC, ADP; ADC; ADCC; see Figure 3) of action at once in a natural-specific way and not only one or two of them. The correlation in Figure 4 would slightly suggest that the complement system (CSC) and phagocytosis (ADP) could help in PFS, ORD, and ORR. Due to this promising reason, let's have a closer look at both CSC and ADP: Admittedly, the relevance and role of CDC in mAb-therapy is still not fully resolved, remains controversial, and requires more research by more postdocs made to PIs. The ratio of PI or faculty to all Ph.D. positions and its R0 birth number [26] is extremely alarming in the US [27], Germany and Europe today and an evidence for the need of these claims, while postdocs are also blockaded everywhere else [28]. CDC is mediated by the membrane attack complex (MAC), which is tightly controlled by regulators of complement activation (RCA) that are sometimes upregulated in cancer [29] and drive mAb-efficacy and can also amplify inflammation under specific circumstances. Hence, a better understanding of MAC and RCA in mAb-cancer therapy could be crucial to further advance and optimize recent and future strategies. Hire postdocs to lead the way.

The regulation of the complement system (CS) and the modulation of its activity in mAb cancer therapy has been of some major interest [29]. CS activation of anaphylatoxins (C3a, C4a, and C5a; acting via rhodopsin-type receptors) can bridge, together with opsonins, the innate with the adaptive immunity (Fig. 3). This illustrates again that a complex interaction and regulation takes place in many smart interfaces called ITSs (immune-tumor-synapses; Fig. 3) that need a new thinking for smart and complex targeting.

Still, the main research interest has resided in modifying the immune response and modulating the complement system and its three main branches: (a) classical, (b) lectin and (c) alternative, e.g., via (i) regulation of membrane-bound or soluble RCAs, (ii) mAb-engineering, and (iii) combination strategy (9;

figure 2). It has been possible to bioengineer mAbs with enhanced ability to recruit the complement system that mediates effector functions [30] but this could require additional efficacy and safety steps, for instance, to restore ADCC that might be affected and to reduce SAE and inflammation that might be higher in such mutations. A $100 bn sector was enabled by the FDA/EMA before the basic research was ready to fully understand all mechanisms and options. Today, publications are even declining (Fig. 5). Table 3 gives another detail overview of the approved monoclonal antibodies in cancer therapy. Only unbiased researchers, postdocs, and firms will be able to unleash the power of such mAb-therapeutics if innovators, researchers and intrapreneurs (17) are hired in sustainable career paths and without excluding anyone. mAbs that act more natural might have more benefits but natural can be also engineered in many ways - a typical project for a postdoc to start as PI: you must build many postdoc career paths.

Table 3: Approved mAbs for Cancer Therapy, very rough efficacy/SAE estimates, no liability assumed

Brand	INN	Target	Clinical Trial Efficacy CI 95%	SAE	ORR	ORD	PFS	ADC	ADCC	ADP	CDC	Cytotoxin
Rituxan®	Rituximab	CD20	FL CLL-ORR8:9-13% (12%-13%) PFS+5-8 CD20-fNHL-ORR12:48-64% CR6 PR42 PFS+12 CD20-dlNHL-ORR24:9-11%, ORR8:37% PFS+8	80-90%, immunologic disorders 9%, G3-4	12,56, 10, 33	14,6	6,5	1	3	2	3	unconjugated
Herceptin®	Trastuzumab	EGF:HER2	CH+AB HER2-BC-ORR13:(52%)+9% OSR but not significant CH+AB HER2-BC-ORR14 HER2-GC-ORR2-3:27% PFS2-3	10%, up to 40% immunologic disorders	9, 27	7,5	2,5	1	3	2	1	unconjugated
Mylotarg®	Gemtuzumab ozogamicin	CD33-ADC	AML: voluntary withdrawn; lack of evidence of efficacy, comb.+induc.new-AML-ORR: PFS8 OSR+1.3 CD33-AML-ORR8:44% PFS8 OSR+1.3	15-30%; hepatotoxicity, hemorrhage, ..	44	8	8	3	1	1	1	calicheamicins DNA-ds-breaks
Campath®	Alemtuzumab	CD52	B-cell-CLL-ORR3:42% PFS+3	97% immunologic disorders	42	3	3	1	3	2	2	unconjugated
Zevalin®	Ibritumomab-tiuxetan	CD20	CD20+-B-celland rituximab-ref.NHL-ORR8-14:24% PFS20	>40-50%	24	10	20	3	2	1	2	isotope, Y90 In111 beta
Bexxar®	Tositumomab /+I-131	CD20	CD20+ fol. B-cell NHL-ORR12:47-64% CR:20-33% PFS+12 relapsed or refractory; discontinued 2013	96%, unclear reason of discontinuation grade 3/4SAA; sales?	55	12	12	3	2	1	2	unconjugated and isotope I131 beta
Avastin®	Bevacizumab	VEGF	see div. cancers AURELIA strat. ORR9:23% PFS3-4 (2.1-3.8) OSR+3 n.s.	ca. 33%, B-pressure; 10x intraoccular inflammation	23	9	3,5	3	0	0	0	angiogenesis inhibitor, unconjugated
Erbitux®	Cetuximab	EGFR	K-ras-wt, EGFR+mCRC-ORR+1-4:18% PFS1-2 OS1-4 n.s.; recur. Metas. head/neck cancer-ORR+1:20% PFS+2 OSR+3	>25%-90%, nausea, anemia, vomitting acneform rash, ...	19	2	1,5	3	0	0	0	EGFR inhibitor, unconjugated
Proxinium®	Proxinium	EpCAM	adv. reocc. head/neck cancer ORR3:40-43%	10%? preliminary	43	3	3	3	0	0	0	EF2 inhibitor, cytotoxin
Vectibix®	Panitumumab, ABX-EGF	EGFR	pre-treat. wt-K-ras mCRC-ORR3:22% OSR4 PFS-1+1 n.s.	90% dermatologic toxicity	7	3	-1,1	3	0	0	0	EGFR inhibitor (ras,raf, mek), unconjugated
Removab®	Catumaxomab	CD3, EpCAM, Fc	ovarian cancer-ORR3:28%PFS+3; discontinued in EMA	40-80%, abdominal pain	23	3	3,3	1	3	1	1	unconjugated, CD3-TC-engager
Arzerra®	Ofatumumab	CD20-CDC/ADCC	ref. and untreated -CLL-ORR6-7:42% PFS9	67-94% immunogenic	14	6	9	1	3	1	3	unconjugated
Adcetris®	Brentuximab	CD30	pcALCL-ORR4:44% PFS13 CR14	20%-40%, annemia, neuropathy	44	4	13	3	0	0	0	vedotin/MMAE, maleimide
Yervoy®	Ipilimumab	CTLA-4	ORR11-12:5 PFS11-12 OSR+4	30-80%	5	11,5	11,5	0	3	1	1	modulator ADCC enabler, unconjugated
Xgeva® Prolia®	Denosumab	RANK: RANKL	tumors, bone, giant cells ORR3:25% PFS0 higher mortality	30-50%, general	25	3	3	3	0	0	0	RANKL inhibitor, unconjugated
Perjeta®	Pertuzumab, 2C4	HER:HER2	MBS+BC-ORR8:11% PFS6	30-50%, diarrhea, neutropenia	11	8	6	3	2	0	0	RTK HER2 inhibitor, unconjugated
Kadcyla®	Trastuzumab-emtansine	T-DM1-HER2	ORR6:13% PFS3	25-40% fatigue, nausea	13	6	3	3	1	0	0	RTK HER2 inh. emtansine DM1
Gazyva /+ro®	Obinutuzumab , GA101	CD20	CLL-ORR16:45% vs chemo PFS16	0,6	45	16	16	1	2	2	2	unconjugated
Blincyto®	Blinatumomab	CD19/CD3 engager	HL-ORR7:73% (65%-83%); CR32%-21m; PR4-40% PFS8 ref-sALCL-ORR13:86% (77%-95%); CR13-57%;PR2-29% PFS8 pcALCL-ORR4:44% (40%-47%); PR-14%-4m; PFS17	31%; neutropenia, periph. sens. neuropathy	71,84, 44	7,13,4	8,8,17	1	3	1	1	CD3-T-cell engager
Keytruda®	Pembrolizumab	PD-1	Melanoma-ORR3:21% CR3 PR23 PFS0 OS7-10% NSCLC-ORR1:17% PFS4 OS15-17	20-40%, fatigue	21,17	3, 1	0,4	1	3	1	1	PD-1 immune checkpoint blocker
Cyramza	Ramucirumab	VEGFR2	GC-ORR6:12% PFS1-2 OS2	5-50%	12	6	1,5	3	0	0	0	angiogenesis inhibitor
Sylvant®	Siltuximab	IL-6	ORR(3-4, NR): 23% PFS8	20-30%, dermatologic	34	3,5	8	3	0	0	0	IL-6 inhibitor
Darzalex®	Daratumumab	CD38	relapsed/refract. MML-ORR7-8:31	33-50%, pneumonia,	31	7,4		1	3	1	3	unconjugated
Emplicity	Elotuzumab	SLAMF7	MM-ORR2:13% PFS5	65%-75% (+10%) infusion rx	13	2	5, 12, 14	2	2	1	1	immunostimulatory
Portrazza	Necitumumab	EGFR	SNSCLC-ORR:2% PFS3	30-90%	2	3	0	1	2	1	0	EGFR inhibitor

Opdivo	Nivolumab	PD-1	previously treated metastatic melanoma-ORR6:32% PFS3	42-65%	25, 32	6	3	3	1	1	1	anti-immuno-checkpoint blocker
Unituxin	Dinutuximab	GD2	NB-ORR1:15% EFS 25%	25-50%; infusion r.	15	1	25	1	3	1	3	unconjugated
Lartruvo	Olaratumab	PDGFRα	tumors/cancers-ORR6-48:11%	50-90%	11	6,48	4	3	2	1	1	PDGFR inhibition
Tecentriq®	Atezolizumab	PD-L1	NSCLC-ORR10:25% PFS2	53-80%, fatigue,..	25	10	2,NR	3	2	1	1	blocks PD1/PD-L1/ CD80 checkpoint
Bavencio®	Avelumab	PD-L1	NSCLC/tumors-ORR12:33	53-75%, fatigue,..	33	12	11	3	2	1	1	blocks PD1/PD-L1/ CD80, checkpoint inh.
Imfinzi®	Durvalumab	PD-L1	Carcinoma-ORR:13%	96%, fatigue,..	13	12	11	3	2	1	1	blocks PD1/PD-L1/ CD80 checkpoint inh.

* rough estimates, no liability assumed, only estimates, numbers can much vary per indication in case

In comparison to mAb-strategies that might be more artificial and that might lack a natural pathway and an activation of in vivo immune-logics to fight cancer, i.e., a natural workflow and mechanism of the immune system, the next three chapters will deal with more natural ways of activating the immune system, but at much lower concentrations than mAbs (ca. 1-15 mg/kg), which is still less than 0,1% of antibodies in the blood. More natural mechanisms might be activated by adoptive cell transfer (chapter 2), cytokines and co-stimulatory pathways (chapter 3), or by cancer vaccines (chapter 4) that activate the entire immune system. One could project that a combination of all methods could yield a higher efficacy if done right and that is why the field will strive for new combinatorial solutions.

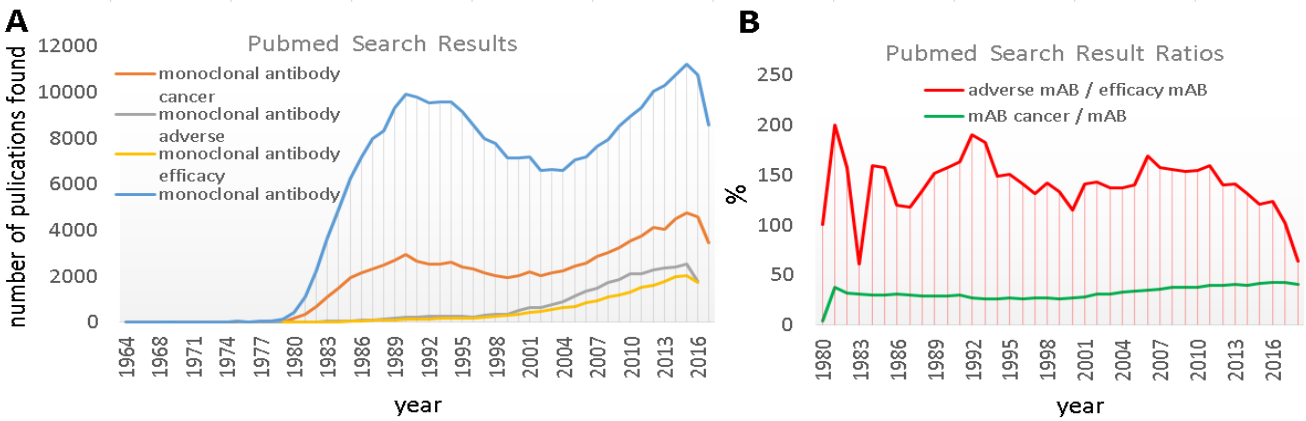

Figure 5: Pubmed search results for mAb in cancer, shown as publications per year. A: keyword "monoclonal antibody", "cancer", "adverse", "efficacy"; B: ratios of adverse mAb and efficacy in %, "mAb cancer" and "mAbs" in general.

Chapter II

V. Adoptive Cell Transfer (ACT)

In comparison to mAb-cancer therapies, it could be increasingly possible for immune-cellular cancer therapy to achieve a stronger coordination and more native or natural forms of ADC, ADCC, CSC, and ADC – in theory. Biomedical strategies of modified immune cell transfers, known as adoptive cell transfer (ACT) activate immune cells, which are believed to be mainly T cell effector cells (but it could also be different cells, postdocs could test this as PIs - there are so many things that are still not checked, e.g. cell states). The activation of immunity on the cellular-level could comprise more of the natural immunologics, i.e., the endogenous pathways and cellular mechanisms of the patient's immune system for targeted cancer therapy. In cancer immunotherapy, adoptive cell transfer (ACT) is simply and broadly defined as "the procedure of transferring immune cells into the cancer patient to cure an oncologic disease". This immune cell transplant offers the great potential and opportunity of gene therapy, pre-treatments, pre-adoption, and conditioning of the immune cells. ACT can be (i) autologous from the patient's own or host cells, (ii) it can be allogeneic, i.e., from a different donor, or (iii) syngenic from genetically-related or identical donors. Generally summarized, autologous cell transfers are often conducted in a semi-syngenic form of related donors and are more safe from SAE due to less graft-vs.-host-disease, but in leukemia, the clinical practitioners sometimes also chose the opposite, as an allogeneic transplant can help to fight cancer via the graft-vs-leukemia effect (GVL) but bears higher risks of graft-vs.-host (GvH) disease due to the graft-vs.-host effect (GvH).

After the discovery of immunization, and post-1960, of T-lymphocytes (T cells) that mature in the thymus and B-lymphocytes (B-cells) that mature in the

bone marrow, and after the 70s and 80s when the antigen-specific T cell reactivity, the T cell receptor (TCR) and its antigen-presenting was found, on MHCs in the mouse and on HLA in humans [1], biomedical researchers began to design rational immune-cell strategies that use T cells and immune cells in ACT [31] to treat diseases like cancer [32].

Table 4 gives an overview of recent immune-cellular ACT strategies: cellular, synthetic and genetic. APC, antigen-presenting cells, display or present antigen on MHC2/HLA proteins (signal 1) and CD28 for APC B7 (signal 2) to activate T cells [2] and there is a cytokine signal 3 (summarized in figure 7). Helper T cells recognize these protein fragments and peptides via CD4+ co-receptors and stimulate killer T cells, B-cells, and phagocytes. Killer T cells are activated by the T cell receptor (TCR) which binds MHC1 and CD8, cognate antigen-bearing-co-receptors, and matures and travels through the body until its TCR binds to antigen and releases cytotoxins like perforin that perforates the cell-membrane for ions, cytotoxins, granzymes and granulysin. HLA histocompatibility and complex molecular machinery discern host and foreign cells [33] and the protection of host cancer cells is a key biomedical challenge of ACT and immunotherapy.

Table 4: Summary of Recent Immuno-cellular Strategies to Fight Cancer via ACT: Synthetic vs. Genetic

Types of ACT	**Synthetic Engineering**	**Indications**	**Approved**
(1) Synthetic ACT	*Constructs*	*Cancer Types*	*Status*
CAR T: Chimeric Antigen Receptor T	Chimeric mAb and TCR-genes in peripheral T cells; "Gene Therapy"	leukemia, cancers	Yes, FDA
TIL: Tumor Infiltrating Lymphocytes	T cells that were grown from the tumor itself; in clinical trials	melanoma, cancers	N/A, ongoing clinical trials
Auto-ACT: Autologous T cell Therapy	Endogenous Tumor-specific T cells grown from the blood	all cancers, less common	N/A, still pre-clinical
Allo-ACT: Allogenic T cell Therapy	Tumor-specific T cells grown from a different blood	all cancers, not common	N/A
TCRs: TCR Transduced Cells	Engineered TCR gene in peripheral T-cells	all cancers, in theory	N/A
HSCT: Allogenic Transplantation of HSCs	Graft-vs-Tumor vs Graft-vs-Host; "unexhausted T cells"	leukemia, HL, NHL, MM; seldom: NB, testicular c.	Clinically practiced
HSCT: Autologous Transplantation of HSCs	No Graft vs. Cancer Effect; HSCS Reconstitution	leukemia, HL, NHL, MM; seldom: NB, testicular c.	Clinically practiced
Synthetic ACT: Any ACT Related Gene Constructs	Tremendous possibilities of combinations for all cancers	all cancers, in theory	N/A
(2) Genetic ACT	*Genomic Engineering & Repairing*	*Cancer Types*	*Status*
EDIT-ACT: CRISPR, TALEN, … "mainly mutation-based"	Engineering of the genome, no constructs or new genes	some cancers, still a theory	N/A

ACT has a major focus on T cells, helper T cells, killer T cells, and gamma delta T cells, which are part of ADCC, the cell-mediated immune responses, but could theoretically and practically also include further humoral B-cell strategies that work together with T cells and hereby unfold synergies. Therefore ACT could theoretically become much bigger in the immune-oncology market that is believed to grow to $100 bn by 2022 [12]. ACT using autologous tumor-infiltrating lymphocytes was seen as the most effective treatment in 2008 [34], while the treatment of solid tumors is still less developed but believed to also be promising [35].T cell activation specific for tumor-epitopes or peptides is seen as a potential route to improve clinical outcomes, as T cell activation correlates with improved health outcomes in infectious diseases [35] and is known to play a role in syngenic cancer immunity and later from ACT research [8], [19], [36].

Synthetic biology offers a tremendous amount of new strategies that are still poorly explored for ACT [36] likely more than pure genomic studies (Table 4). But synthetic biology is the combination of molecular biology, genomics, and cell biology, what business and HR people tend to oversee, and they should hire more molecular biology postdocs. At least in our times with limited knowledge of how to best heal the cancer genome phenotypes and genetic diseases in general, synthetic biology offers more possible solutions,

mechanisms, and combinations to be tested. One of the high potential technologies and methods of ACT termed CAR T has now, very recently, been approved by the FDA. CAR T stand for Chimeric Antigen Receptor T, which is a hybrid construct of an antigen receptor that binds the cancer epitope via a binding fragment and intracellularly activates the transduced immune cell to fight the cancer cell (Figure 6). Approvals of CAR T strategies by the FDA since 2017 have yielded two new historic milestones: Kymriah (tisagenlecleucel), and Yescarta (axicabtagene). Simultaneously, these FDA approvals have also granted the first officially approved US gene therapy which could mark a new area of biomedicine or its slow rise (Table 5, Figure 6). Noteworthy, transplantation of HSCs in leukemia is also an ACT practice by definition that predates CAR T (Table 4).

There are many recent advances in T cell-related ACT [37], [38]. A new interesting and life-saving parameter could be the quality of immune cells that are subjected to all forms of ACT in general: for example, it could be recently revealed, for the widely common HSC transplantation approaches in leukemia therapy, that "exhausted" PD-1hiTIM-3+ T cells associate with and clearly predict AML relapse post allogeneic HSC transplantation [39]. This has some major implications for ACT in other strategies and settings like CAR T. Thus, it might be always very important to have unexhausted and high-quality T cells of a specific state in ACT, as T cell exhaustion of the graft correlates with relapse [40]. This seems not to be tested according to the FDA labels of the two new CAR T drugs and it could save patient lives if it would be tested, as the success of the procedure correlates with the expansion the CAR T cells and their state – and future cell based transplantation therapies should now include the quality of the molecular biological states of the cells and unexhausted expansion (molecular cell quality control, MCQC).

Another highly promising ACT-strategy that has been termed TIL, i.e., tumor infiltrating lymphocytes (Table 4) has shown a very high potential for metastatic melanoma [41] also in clinical trials, but it has still not been approved by the FDA or EMA in early 2018 (Table 5). Another very promising ACT strategy and ACT case had been UCART123 from Cellectis S.A., a CAR T targeting CD123 in BPDCN in patients with refractory or relapsed blastic plasmacytoid dendritic cell neoplasm- before it was stopped by the FDA after one patient developed a cytokine storm. This again illustrates the need to research the mechanisms in more depths. Importantly, cytokine release syndrome (CRS) [23] has also occurred in patients receiving Kymriah™ and Yescarta™, including fatal or life-threatening reactions, according to the most recent FDA label. Table 5 shows the two recently FDA-approved ACT biomedicinal CAR T products with some more detail. Cellular states, efficacy and off-targets of ACT should be further researched by more postdocs and PIs. There are very many combinations of ACT possible and very much preclinical research is still needed to find the mechanisms and therapies.

Table 5: Approved Immunocellular ACT Cancer Therapy in 2017/2018: Signs of a CAR-T Breakthrough

ACT-Type	Brand, Firm	ACT Name	Indications, Specifics, Cancer-Subtypes	FDA	EMA	ORR	Response	DOR	PFS	OS	Sales/p Cost/p
CAR-T, autologous, retroviral gene-therapy, 2*10^6-8/kg, following chemolympho-depletion	Yescarta-Gilea Kite	Axicabtagene Ciloleucel (KTE-C19)	Target: CD19, CD28/CD3-zeta chimeric antigen receptor, relapsed-type B-Cell Non-Hodgkin, Lymph-oma (NHL) subptype: diffuse large B-cell lymphoma (DLBCL), DLBCL in patients who had follicular lymph-oma, high grade BCL	2017	N/A	up to 72 %	CR: 51% vs. 7% PR: 0%, 21%	9,2	6 vs 3-4 month(Δ 2,5), n.r.	15,4 vs 11,2 month (Δ3, 8), nr	373K$ pot. future peak sales ca. 2.7$bn
CAR-T, autologous lentiviral gene therapy 0,2*10^6-2,5*10^8/kg	Kymriah, Novartis	Tisagenlecleucel (CTL019)	Target: CD19-CD8-alpha-hinge-41-BB-coactivator-CD3zeta juvenile (<20) ALL; Diffuse Large B-cell Lymphoma (DLBCL)	2017	N/A	up to 83 %	up to 83%	nr	nr	nr	475K$* 600 300M/ year

Will this new class of CAR T therapeutics be a new established passable FDA-route like what has happened to Genentech's mAbs (Rituxan, Herceptin) in 1997/1998? There are already roughly 100 CAR T clinical trials with "undiversified strategies", the North American market could yield ca. $1 bn in 2022 and $4 bn in 2022 at a CAGR of 45-55%, the remaining markets depend on regulators like the FDA and EMA in BRICS and

internationally, and Asia. The CAR T immuno-cellular cancer therapies are more "procedural" as immune cells must be isolated and modified: According to the FDA label, Kimrah is prepared from a patient's PBMCs (peripheral mononuclear cells), presumably a G-CSF hematopoietic stem cells (HSCs) mobilization strategy that is usually followed by a standard leukapheresis procedure, which is an apheresis method. PBMCs enriched for "T cells" are then transduced with the lentiviral CAR T transgene, and then activated with anti-CD3/CD28 antibody-coated beads, expanded, washed, formulated in suspension and cryopreserved, sterility tested and thawed before administration. According to the new FDA label, Yescarta is similarly prepared from the patient's lymphocytes using apheresis, the patient's T-cells are activated during a defined culture period with IL-2 and anti-CD3 antibody, transduced with retroviral CAR T vector, expanded, cryopreserved, and thawed before administration. However, only the culture period, not the media is well defined, with respect to the label.

Both procedures are not highly standardized due to the required isolation and culture settings that can cause slight variations as identical results are not possible, which makes MCQC so important. Also a more precise SOP description is missing, like more specific efficacy and safety data. Materials and SOPs would be needed by independent researchers to assay, test and optimize new medicinal ACT procedures in an unbiased and transparent way, which is often not feasible but could also much help the firms without creating any new costs to them. The ACT mechanisms and construct strategies are provided in a general form that is given in Figure 6. It could generally represent a new very powerfull approach, which offers a new platform technology for academic and industry improvement in open science and open innovation for postdocs [42], [43]: stop to blockade this best workforce.

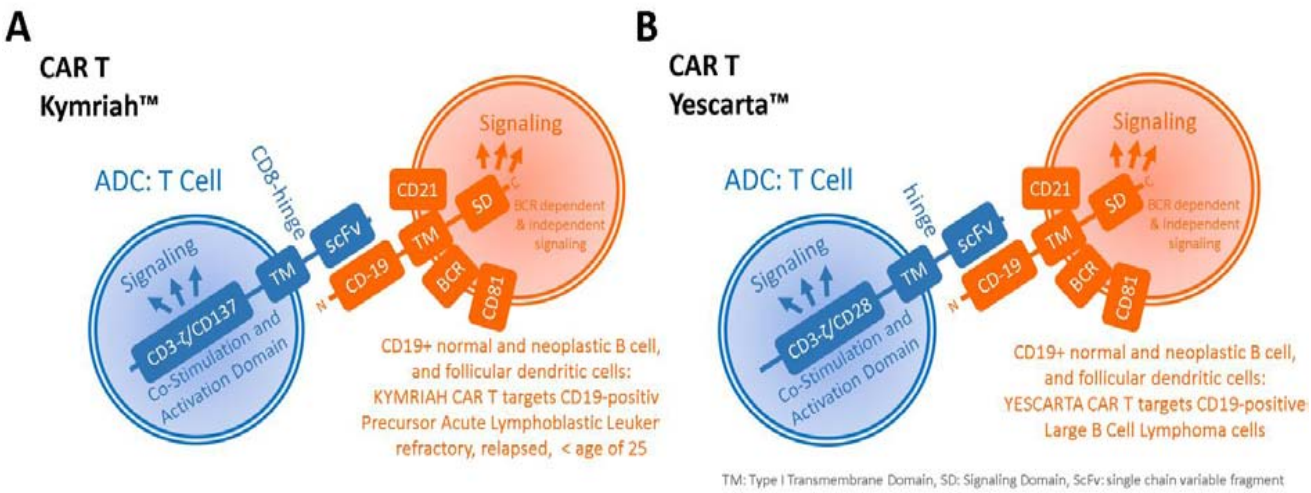

Figure 6: CAR T Mechanism and Construct Strategy of the First ACT Cancer Therapeutics, Approved 2017

What do we really know about the purity of the ACT cells, what do we know about the biomarkers and about the molecular characterization and profiling of these cells before and after CAR-T transduction? The quality of these therapeutic immune cells can be pivotal for the efficacy in cancer and should be better researched, by much more postdocs that are to be made PIs (principal investigators; professors, laboratory heads, etc.). There is really no real need for a further selection of postdocs after more than 10 years of a very harsh, unfair, and challenging negative selections. This really an ongoing big crime against postdocs by the HR procedures in the industry and in academia. (This must be always mentioned at this point to assess the entire situation correctly). It was very wrong to inhibit all postdocs, the most competent applicants, as it hinders breakthrough research and management of growth, also in ACT. Here, researching the key mechanisms of ACT quality would lead the way forward: for example, it was very important to research why some AML patients relapse and die from a stem cell transplant while others did not [39]. FACS revealed that an exhausted" PD-1hiTIM-3+ T cell pools associate with and predict an AML relapse [39]. Whenever T cells are transplanted, it could be tested if they are vital, depleted or exhausted, or still healthy and viably cytotoxic. This could theoretically advance CAR T, ACT, and would save many ACT patient's lives: T cell exhaustion was initially identified in chronically infected mice and subsequently before the molecular immune-signature was found in human cancers [44]. Restoring T cell exhaustion, or isolating, or transplanting unexhausted T cell pools for ACT could be thus promising. Thus, a general strategy could be to assure "marker-quality control and marker programming" that transplanted immune cells are of high quality as indicated by the right epitopes. In fact, respondents of Yescarta™ had higher numbers of anti-CD19 CAR T cells in blood (Cmax 205%, n=73; 43.6

cells/µl vs 21.2 cells/µl; and a 251% AUC, day 0-28) as a result of an initial rapid expansion following infusion, another hallmark of quality – but key biomarkers are not indicated. This shows that viability and non-exhaustion are pivotal for the ORR and that more research about the cellular mechanisms and markers is still needed to improve the viability and duration, which declines to baseline levels after 3 months. Complete remission (<5% blasts in bone marrow) of Kymriah™ was 63% after 3 months, and complete remission for Yescarta™ (2007-CR-criteria not indicated) was 51%. Both first-in-class therapies also show a high overall remission rate of 83% Kimriah™ and 72% for Yescarta™. ORR and CR imply very high efficacies but the OS and PFS data are missing, i.e., not reached.

Now there are two scenarios thinkable: (1) survival is much improved and therapy is a success, or (2) survival is no much improved and therapy not a long-run success but only for 3 months. In other words, the drugs were approved and hit the market and patients before this question is resolved. If the first scenario will hold true, CAR T will have shown to be a very promising new cancer strategy that might be more effective than some mAbs, which could be a disruptive breakthrough innovation for the mAb drugs if they yield lower CRs and ORRs, but it is likely indication-specific. Hereby it could slowly boost ACT at the expense of mAb in the future for for more and more indications - but efficiacy milestones for solid tissue cancers are still more elusive. However, if scenario 2 holds true, it could trigger a slow-down of ACT medicinal product development due to the high risks of CRS [23]. As a result, the OS and PFS in the next years could pull a bn-dollar-trigger. Most if not all first-generation cancer immune-therapeutics cannot fully deliver the wanted OS and PFS duration desired by health care providers and patients, making scenario 2 more likely, but this is ACT, not mAb, and one still must wait and see. There should be a new space for second-generation cancer immune-strategies. For example, in scenario 2 of CAR T cell therapies, mechanisms must be found why OS and PFS are not as responsive as the ORR and CR after three months: why is there a lack of a full eradication of cancer and how to improve the duration. There are clear-cut answers to such questions needed, so enable postdocs in open science projects and academic projects [42], [43].

Table 4 also comprises HSCT, the clinically widely practiced more traditional hematopoietic stem cell transplantations in leukemia and less frequently also in other cancers. Chemotherapy depletion is followed here by reconstitution strategies with allogeneic or autologous HSCs, both bear significant risks and chances. The allogenic ACT graft-vs-tumor (GVT) effect is believed to be mediated by a direct GVT mechanism targeting alloantigens expressed on tumor cells (HLA, and HLA/peptides, or MHC, respectively), and an indirect anti-tumor effect of host CD8+ T cells that could be highly independent of alloantigens [45]. Benefits from inhibitory receptor blockades seem to be still limited here (see Table 3; PD1, PD-L1), which is a more general view (24; see discussion). Recent advances in T cell ACT vaccines require to overcome three or more inhibitory steps and there are four generations of chimeric antigen receptors [37]: mainly the intracellular signaling domain is modularly advanced and elongated: CD3ζ, CD3ζ/CD28 and CD3ζ/4-IBB, CD3ζ/CD28/4-IBB, or promoter/cytokine-inducible CD3ζ/CD28/4-IBB [37]. The bias could be the extracellular domain, the targets, combinations, and immuno-logics. Clinical trials focus much on metastatic melanoma with ORRs in the range of 49-72%, leukemia, but also many other cancers [37].

Chapter III

VI. Cytokines and Co-Stimulatory Pathways

Cytokines and co-stimulatory pathway cancer treatments overlap with all branches of cancer immune-therapeutics (Fig. 1). They act via supportive or inhibitory signaling routes, co-stimulatory pathways to overcome check-points and are crucial for all proper immune-cell responses. Hence, they act at the ITS and interface of immunotherapy and the immune system: they are important for cancer vaccines (chapter 4), for antibodies (chapter 1), and adoptive cell transfer (ADC), as T cell function is regulated by them (chapter 2).

Especially approaches that target signaling proteins like PD1/PD-L1, EGFR, CTLA-4, VEGF, PDGFα/RTKs, IL-6, GM-CSF, and more, are thought to act via modulation of cytokines or co-stimulatory pathways. There is a big overlap with “targeted cancer therapy” and “immune-checkpoint inhibitors” and also ACT strategies have much overlap with cytokines and costimulatory pathways [33]. It connects to basically all cancer therapeutic areas to some extent as signaling is always involved (Figure 7). There are two [2] and maybe additional signals required in T-cell activation (helper T cells and cytotoxic T cells) and three or more big repressions or therapeutic pitfalls to overcome: Signal 1 between a T cell and an APC is mediated by TCR and MHC (HLA) with cognate antigen or peptide. Signal 2 is termed the co-stimulatory signal, e.g., CD28/B7 and PD1/PD-L1, that results in survival, clonal expansion, and differentiation signal 1 and 2 co-activated T cells. Signal 3, supposedly, are time- and context-dependent signals that modulate or guide T cells. Hypothetical signal 4 could stem from yet unidentified cells or cell types to polarize subsets (Fig. 7). Canonical signal 2 amplifies canonical signal 1 and effector T cells subsequently also sustain B7 expression on APCs. Immune tolerance for cancer arises if signal 2 (B7/CD28) is missing, which is inhibited by CTLA4 and PD1/PD-L1 and CTLA4 (Fig. 7), which are thus rational

targets (Table 2), but the ITS and immune cell regulation could be still even more complex (Figure 3). Signal 1 and 2 are direct-immediate while 3 and 4 are more local-global but this can be context-dependent.

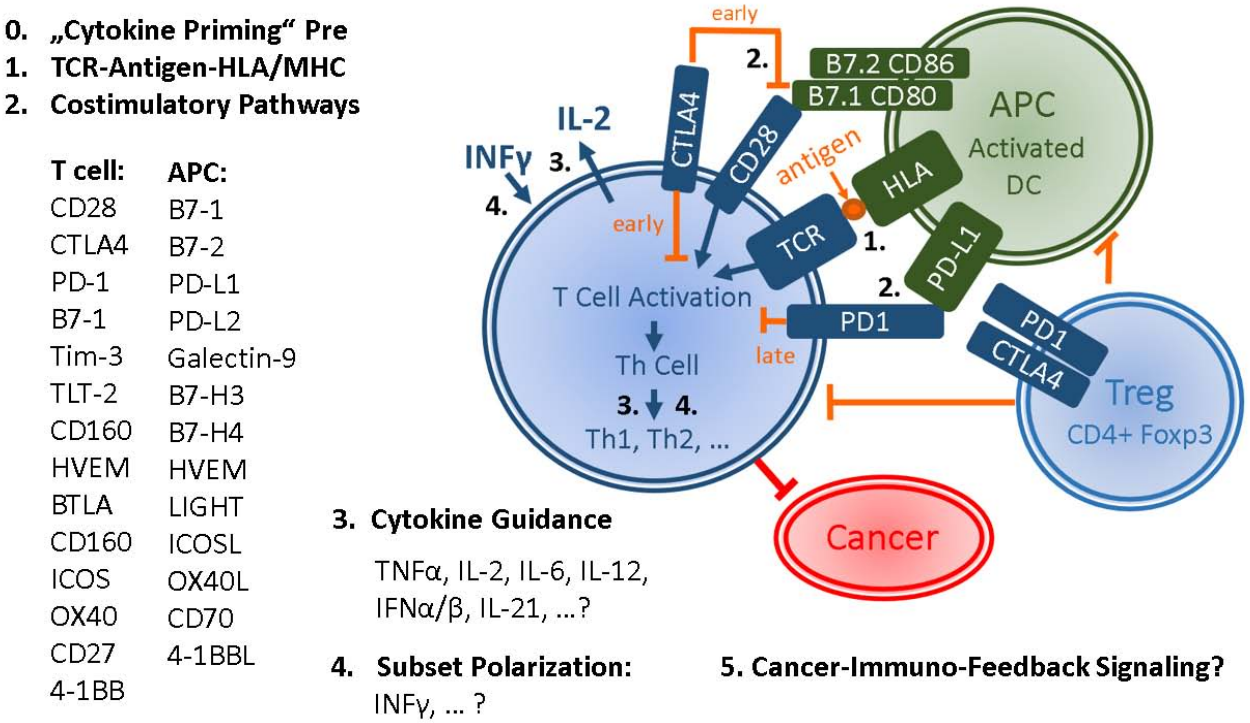

Figure 7: Costimulatory Pathways in the Activation of Helper T Cells in Cancer Immunotherapy

Many current strategies focus on Signal 2, which is important, but could be biased as all signals play a role in immuno-logics and all signals could be more complex: what about all the additional cytokines and co-stimulatory pathways? Signal 2 can act positively or negatively, thus targeted therapy was referred to as immune checkpoint agonists and antagonists ("repressors of immune repressors" to unleash the immune-cancer attack, e.g., PD-L1), while "Signal 3" are context-and-time cytokines that manage immune cells on a different level and subsets like Th1 and Th2 [46]. "Signal 3" could be split into a T-cell initiated "Signal 3" and a T cell receiving "Signal 4" that could also further prime subsets and subset activation by unknown signals and cells. T helper cell activation can be thought in cellular immune models [47], and INFγ could be a signal 4 of unknown cells [47] but also other cytokines and costimulatory pathways that further polarize subsets of immune cells. Even a signal 5 that feedbacks between the cancer cell and the immune cell is thinkable but research is still elusive and again more postdocs should be hired as PIs to research additional signals. They could start as one-man-labs and could work bottom-up into bigger labs in an unbiased way and everybody could get a chance this way while performance could start to drive success and lab growth. Understanding the subset priming or driving mechanisms, co-stimulation, and states, will help to boost CAR T [48].

In analogy to mAb-strategies, cytokines and proteins can also be used in very comparable and targeted biomedical strategies. For instance, cytokine-binding can be used like an antibody-binding to target specific cancer cells or cellular functions: denileukin diftitox (Ontak), for example, is an immunotoxin approved by the FDA for the treatment of refractory T cell lymphoma. It is a fusion of a cytokine, IL-2, conjugated to a cytotoxin, diphtheria toxin, that binds to it IL-2 receptors to target malignant cancers. There are additional examples, like off-label uses, how co-stimilatory signals can be targeted in cancer immunotherapy.

Chapter IV

VII. Cancer Vaccines

The cancer treatment modality of cancer vaccines is also viewed as promising [49] - even since a long time. Cancer vaccines can be grouped into cancer prevention and cancer treatment vaccines (Table 6). Cancer vaccines are still intended to work like in classical immunizations by preparing the adaptive immune system for tumor antigens. Immunization agents comprise: peptides [50], lysates [51], proteins, bacteria, particle and viruses and virus-like particle display (VLPs) [52], DNA [53], [54], RNA [3], adjuvants, prime-boost [53], [54], or living cell-like dendritic cells (DCs) and APCs that overlap with ACT strategies or weakened tumor cells that are not causing any new cancers, e.g., due to irradiation to halt proliferation [49].

The history of cancer vaccines is long and also goes back to Dr. William Colley in 1891 [1], [32], [49] who injected inactivated *Streptococcus pyrogenes* and *Serratia marcescens*. BCG, Bacillus Calmette-Guérrin, is another Coley's Toxin that is still in use as a cancer vaccine, until today [49], for example for bladder cancer. It is a weakened form of a tuberculosis-type bacterium and it is being investigated for other cancers. George Klein has already shown in 1960 that a tumor can be rejected if a vaccine is administered to the same mouse [19]. Terry Boon has subsequently shown that the immune system fights cancer, maybe implying that it only needs more help fighting it efficiently [19]. Despite its long history of efforts, clinical progress has widely been very limited, and the mechanisms should be researched by more postdocs who could figure out how this works: the immunization code is not cracked for cancer, with few exceptions maybe like HPV, and there were still a big reward.

Recently, the FDA has approved immunotherapy-based vaccines called sipuleucel-T (Provenge) [55], which represent a new milestone in the field of cancer vaccines. The vaccination procedures functions in the following way: APC/DC cells are isolated via leukapheresis, isolated and activated in vitro with human recombinant PAP-GM-CSF (PAP: prostatic acidic phosphatase, an antigen on prostate cancer cells), linked to GM-CSF (granulocyte-macrophage colony stimulating factor) an activating immune-stimulant, and infused into the patient three days post cell harvest. The active components of Provenge are believed to be APCs (DCs) and immune stimulant PAP-GM-CSF antigen-activator proteins, so both. Hence, one may speak of the first therapeutic cancer vaccine but it is also an immune-stimulant and one cannot speak solely of a unique efficacy and adverse effects of one vaccine. Immunosuppressive agents are not thought to be administered as they would interfere with the immunization strategy strategy - but one day they might help to co-protect the body during the treatment with highly targeted immuno-adapting approaches.

Combinatorial adjuvant strategies will maybe soon help to overcome the known obstacles to cancer vaccines. Combinatorial treatment with other cancer therapeutic strategies could also be very promising but are research intensive and more senior postdocs should be hired and many more long-term contracts are needed in all fields of science, also clearly in cancer immunology and drug discovery. Additional PI positions are needed to transition the postdocs and the money can stem from smaller labs and better resource allocation via nationwide or regional core and service facilities. Finally, the market of cancer vaccines is expected to grow further from $2.5 bn to $ 7.5 bn in 2022 with a CAGR of 17% and bears very much further potential, especially if the molecular mechanisms will be better understood and better utilized biomedically.

Table 6: Types of Cancer Vaccines

Cancer Vaccine	Specifics	Indications	Approval	Brands
Cancer Prevention Vaccines	***Prevention of***	***Cancer types***	***Cases***	***Cases***
HPC Vaccines	human pappillomavirus	HPC can lead to genital region cancers	FDA	Gardasil® Gardasil 9® Cervarix®
HBV Vaccines	human hepatitis B virus	HBV can lead to liver cancer	FDA, since 1981	Engerix B® Recombivax HB Twinrix, Pediarix Heplisav adjuv.
Cancer Treatment Vaccines	***Treatment of***	***Cancer types***	***Cases***	***Cases***
BCG, Bacillus Calmette-Guérrin Mycobacterium bovis	bladder cancer; functions as an immuno-stimulatory adjuvant "immune-activation"	bladder cancer, and potentially other cancer (researched)	practiced	TICE®
Sipuleicel T APC8015	prostate cancers; IV: 50M/d autologous primed PC, DC immune-stimulant/vaccine; OS: +4 month	hormon-refractory; prostate cancers	FDA, since 2010	Provenge® of Dendron then Valenat; sales ca. 100K$/p
Other Cancer Treatment Vaccines	***Examples***	***Some examples Cancer types***	***Some Examples***	***Some Examples***
Autologous Cancer Vaccines, "personalized cancer vaccines"	patient-derived cancer cells	e.g., tumors, other cancers	clinical trials	Vitespen

Allogeneic Cancer Vaccines	human-derived cancer cells	e.g., tumors, other cancers	clinical trials	Canvaxin™
Peptides clinical examples	e.g., preventing recurrence of breast cancer; Her2/Neu	e.g., breast cancer, etc.	clinical trials	NeuVax from Galena Biopharma
DNA clinical examples	e.g., DNA targets hTERT	e.g., intramuscular IV, many cancers	clinical trials	INO1400 from Inovio
RNA clinical examples	e.g., mRNA-based-targets	e.g., melanoma and other cancers	clinical trials	gp100-mRNA
Particle clinical examples	particle-adjuvants; VLPs, etc.	e.g., breast cancer, anti-relapse etc.	clinical trials	e.g., Her2/Neu
Prime-Boost clinical examples	(a)heterologous (b)homologous	e.g., DNA; increased TCR avidity; CRC	clinical trials	e.g., GUCY2C-PB CRC
Tumor cells clinical examples	e.g., TCs also secrete GM-CSF	e.g., pancreatic cancer, clinical trials	clinical trials	e.g., GVAX
Cancer Lysates	e.g., wide variety of Ags/MHCs	e.g., melanoma and other cancers	clinical trials	e.g., TRIMEL, TRIPO
Viruses: e.g., HSV clinical examples	e.g., Talimogene laherparepvec	e.g., melanoma and other cancers	clinical trials	Oncovex (T-Vec)
Immune Cells: APCs: DCs/TAP cells	overlaps with ADC strategy	see ADC examples	clinical and FDA	e.g., Provenge (FDA)
Combinations of many individual strategies	e.g., PrimeBoost or Protein and DCs	very many combinations are possible	Clinical and FDA	e.g., Provenge (FDA)

VIII. Conclusions: Bias in Cancer Immunology

This review reveals how important it is to see the big picture and to get an overview of all trends and developments, both quantitatively and quantitatively, in science and management - and with a focus on the key driver of success: (i) postdocs and sustainable career paths for scientists, (ii) better regulations and incentives, and (iii) a more balanced ambidexterity of the sector, regulator, and strategy. This is equally important for an unbiased understanding and innovation and decision making in the biopharmaceutical sector. Only a holistic review approach with all revelatory listings can make the prevailing biases become directly more apparent, and there are significant biases in today's science, innovation, and job market [56]-[60]. This review summarizes all most important advances and progress in cancer immunology and thereby finds several biases in all clinical fields denoted as 10 biases of cancer immunology and biopharma sector in general:

1) A lack of diversification, not of postdocs that are all universal-specialists and transferable experts, but a lack of diversification of biotechnological and biomedical strategies of firms, and a further concentration of firms and mono-strategies due to M&As, ideas, patents, network-like monopolization in all markets and clinical trials; a clinical and medicinal product licensing focus on biologicals for only few rational cancer targets, and only few biomedical strategies despite of the vast amount of promising therapeutic possibilities still to be explored and exploited (e.g., EGFR, PD1/PD-L1, CD20, and simplistic mAbs-strategy in general: injection of mAb at high doses).
2) A bias toward strategically hindering the best biomedical researchers [27], [28], [61], i.e., senior postdocs, experts from all related fields; this is a breach of the UN human right to work of postdocs, in science, by many western countries (USA, Germany, EU, Switzerland, UK), discriminated based on years of experiences yielding top-level skills, hence a quick change is needed also not to steadily break the constitution of these countries that formally assure human rights also for postdocs.
3) Low-efficacy-bias: the relation of a $50-100 bn market with efficacies only in the range of month still bears some bias to overcome; this could provide bad incentives for future cancer therapeutics that save decades of lifespan. How to unbias the markets for second-generation drugs in the future that extend the lifespan for years, remains a key question that must be answered soon.
4) Adverse-event-bias: due to the high SAEs and adverse events in cancer therapeutics, innovation in cancer immunology might be biased towards higher SAEs or AEs than would normally be allowed by the FDA or EMA; reduction of SAE and cytokine storms via more new research also makes much sense for corporations that invest in clinical trials [23]. The

hiring of more senior postdocs could improve the cost/benefit ratio and the assessment of the FDA and EMA for many additional drugs; they can reduce the costs per innovated new cancer drug and can help convert SAEs into higher efficacies by reducing the biases.

5) Cancer-marker-, target-, indication-, and exploitation-bias: there are many more cancer biomarkers and cancer mechanisms that could be utilized for targeted therapy. Thousands of clinical trials only center around comparatively very few medicinal products, targets, and strategies (Figure 2); targeted strategies for indications are missing; this clinical bias follows a prevailing market logic that goes back to the patent procedures and sales imperatives in times of assured exclusivity of the medicinal products. Making sales reach as many cancer segments as possible in roughly 20 patent protected years is often the main commercialization idea that could have caused this clinical and R&D biases; cooperation between big players defines the game and might slow-down best and new and also disruptive R&D innovations of real breakthrough.
6) Scientific and mechanistic biases in immune cell effector mechanisms that stem from the markets: e.g., the correlation (Figure 4) reveals that mAbs could show a more valuable efficacy if CDC and ADP are activated in concert with ADC and ADCC (Figure 3). The more natural the therapeutic mAb resembles and activates endogenous antibody effector mechanisms, the better it might be (mAbs simulate endogenous mAbs): direct coupling of cytotoxins to Fc parts might sterically und structurally interfere with ADCC, CDC and ADP mechanisms, which could be an unnecessary bias and can be improved; mAb could be advanced via Fc engineering [25], "educated-sophisticated strategies" screened.
7) Clinical-trials-bias: billion dollar conflicts of interests might still hamper an unbiased research setting; blinded and double-blinded studies might not be unbiased enough in times of collective mental intuition and cognitive biases; lack of independent reproducibility, lack of secret default clinical phase IV studies to validate all phase III studies; lack of clinical trial data transparency, access, and reporting due to the conflict of intelectual property rights and the right to be informed as a patient.
8) Translational-R&D-bias in relation to clinical trials and clinical outsourcing bias of clinical trial research data into translational research that is might be also not fully reported in clinical trials; lack of independent translational research, lack of access, lack of funding, lack of transparency.
9) mAb-bias: a potential bias towards monoclonal antibody strategies that are found by a comparison of all four chapters, see figure 1: mainly mAbs are dominating the clinical trials and the markets, although immunological mechanisms like vaccines and ADC should might bear an equal potential , at least in theory. Can this be a natural bias? This raises the question, why did the mAbs and co-stimulatory pathways work faster, while cancer vaccine theory exists for 100 years? One of the reasons for this time-bias, this review suggests, is the sweeping incomplete understanding of all immunological mechanisms that are always or can be involved. They are not fully harnessed by all of the approaches an there is still room for biomedical improvement to be explored, which should be done by hiring more postdocs and by creating more unbiased PI positions than available today.
10) Finally, one might speak of a breakthrough-blockage bias that dominates research everywhere like a "conflicts-of-interests-bias" that mutually blockades postdoctoral researchers, which are PIs without PI or faculty position but often have top talents and skills far above the regular PI-level. This bias is long known in the field of innovation where all innovators and scientists are usually hindered also in firms: barriers to intelligent intrapreneuring, innovation, and good ideas [17]. Due to the artificial scarcity of postdoc opportunities (they are illegitimately discriminated once they have valuable experiences and competencies by all prevailing HR procedures) and the R&D-portfolio-and-investment-bias, a lack of diversification in R&D, fancy but sometimes also misleading cutting-edge technology trends, the whole sector experiences soaring costs per drugs developed. Investing in postdocs would make more sense, if done right (all could focus on the science again once this issue is solved). More postdoc job, more projects, more intelligent ideas, and more unbiased promising immunological and therapeutic mechanisms are needed in the portfolio and are still needed by patients.

In summary, to do good science and cancer immuno-therapeutics, these managerial questions must be solved by normalizing these 10 biases. The cancer immunology markets have begun to boom, while the immunological mechanisms are not fully resolved, which is still needed. Better ambidextrous balances between exploration, and exploitation [15], efficacy and adverse effects, efficiency and effectiveness are needed and recommendable. New and more dynamic opportunities, threats, strength, and weaknesses have emerged that makes cluster research, staff and postdoctoral intrapreneuring and postdoctoral intrapreneuring, GSI and ISF, an inevitable task and advisory discipline [17], while a greater range of medicinal and biomedical research toolsets are now available blazing the trail to more "combinatorial cancer treatments" that bear potential but might again reduce the diversification of the first-step R&D portfolios. ACTs and vaccines

became more readily available and CAR T is the next big milestone and breakthrough and the next two years will be decisive for its market future, the EMA, FDA, and ACT innovations in general. Eventually, the scientific field, the biopharmaceutical firms, the regulators and the entire research community can best move forward if we assure settings that allow more unbiased ways to go and sustainable career paths for all.

IX. Biomedical Outlook

New mechanisms, new targets, and combinatorial strategies will be a linchpin of future progress but the centerpiece will most likely stay defensive non-diversified strategies and they will move too early, and maybe too unprepared by preclinical research, into combinatorial cancer treatments, while postdocs are “the most educated workforce” and would very much help lead the right way. In fact, combinatorial strategies will be important but there are a plethora of possible combinations that seem to require more preclinical testing, more educated guessing and more rational studies. New aims will comprise to even more combine the different immunotherapy options and conventional treatments, but a preclinical screening for rationals could be also helpful to treat indications: biomedical strategies can still be more explored before they become prioritized in a more unbiased way: to best treat indications, with whatever will work best. In the scientific details, some will try to advance and enhance function of effector T cells via Tregs (OX40, CCR4, GITR, CD73), Teff (CTLA-4, PD1/PD-L1, LAG3, OX40, 41BB, ICOS, GITR)s, and myeloid lineages (TLR-7/8/9, IDO, CSF-R1, CD40) [62] and new stratified strategies for personalized immunotherapy will arise [62] especially when better diagnostics and customized treatments become available in “stratified cancer therapy“. Developing new anti-cancer drugs is extremely time and cost-intensive and “progress to build on” is very important and must be more acknowledged and valued, like fair platforms of innovation for postdocs and open science [42], [43]. Repurposing of mAbs is relatively cost effective but the right treatment combination and biomedical strategy cannot simply be found only by testing for more indications and require diversified research strategies, rational strategies, strategy screening, and educated guessing. New cocktails for anti-cancer treatment could include many biologics at once to fight refractory cancers with specific drug resistances. Hundreds of promising factors have been described including candidate genes, proteins, metabolites, RNAs, or miRNAs and many more. They could be explored as they have not been suitably tested and screened in pre-clinical settings. There are also some mAbs that are highly promising in the mouse model and are not followed up upon by the industry due to unknown reasons. New targets could be both, extracellular or intracellular, targeting the tumor, the tumor niche, or enhancing the immune system against the tumor, which would be summarized as “rational combinatorial targeted therapy”. Favorable toxicity and efficacy profiles of monotherapies for a wider spectrum of cancer can now be combined in more rational and more educated approaches. There are many clinical trials [63] and R&D ways new R&D ways of testing and potentially more intelligent ways to narrow the options down for better outcomes in combinatorial treatments. Defensively, biopharma starts to combine mAb immune checkpoint inhibitors (e.g., PD1 or PD-L1; mAbs: Nivolumab or Pembrolizumab) and ALK/EGFR TKIs in advanced NSCLC; or mAb immune checkpoint inhibitors with antiangiogenics [63]. Still, the big future of “rational combinatorial targeted therapy” has yet to come and the exploration of millions of potentially promising options has just begun. A catalyst that massively speeds up all of these developments is “fair chances for postdocs”.

The right combinations pose a new risk to researchers and the health care system the health care system – what if they are not made public? Antibodies and single products are a bit more transparent for the FDA, EMA, and government, but combinations of cancer treatment can become a monopoly secret of a conspiring medicinal network. Why should a conspiring network make the best solutions public if the firms do not have an incentive? Also, what if the healthcare insurers cannot cover skyrocketing cost combination, and when will these combinatorial treatments start to become more affordable who can assure a healthy market. How to assure that best medicine are also sold?

Research networking, advisory networking, and clinical trial networking somehow exist everywhere. In trials, they share expertise, information, hidden clinical and procedural ways and agreements, samples, and data through research and clinical trials networks that should foster clinical development and are public. Only as a prominent example (not saying if this is good or bad, but trying to reveal the hidden network power of influence that has grown and could be uncontrolled) the NCI supports efforts towards collaborations with extramural researchers on immuno-therapy comprise the CITN (Cancer Immunotherapy Trials Network), the Experimental Therapeutics Clinical Trial Network, the National Clinical Trial Network, the IOB, the CTEP, CIMACs, CIDC, the Cancer Moonshot, the Immuno-Oncology Translational Network, the Pediatric Immuno-therapy Discovery and Development Network, the PACT and even more. Networks strongly influence (this can be both positive or negative in theory) every clinical study, but also professor and PIs network, and firms “strategically cooperate”. Altogether, there is a network that blocks most postdoctoral careers by sabotaging all "HR thinking and job criteria" in the industry and in academia. This has slowed down a bigger breakthrough and more progress in cancer immunology and the rise

of the century of molecular biology. This causes a cognitive network bias of all actors in science [59]. These networks and consultancies have hindered postdoc career paths and leadership in the biomedical sectors, biomedicine and cancer immunology. Also, more and broader open science preclinical research should better connect to the clinical pipeline.

Thus, this work finally concludes that there is good and evil networking in the world and in the sciences, the first is the prerequisite for good sciences and best biomedicines, the second is the opposite and ends all sciences and our modern enlightened world.

Hence, we must assure good networking and advice and prohibit bad networking and advice, everywhere. This can be done in open science and open innovation [42], [43], and is a prerequisite for the discovery and development of better therapeutics, especially also in cancer immunology.

List of Abbreviations

A: year, ACT: adoptive cell transfer, ADC: antibody-dependent cytotoxicity, ADCC: antibody-dependent cellular cytotoxicity, ADP: antibody-dependent phagocytosis, ALCL: anaplastic large-cell lymphoma, AML: acute myeloid leukemia, BCG: Bacillus Calmette-Guérrin, BPDCN: blastic plasmacytoid dendritic cell neoplasm, Bn: billion, CAGR: compound annual growth rate, CD#: cluster of differentiation, #: number, CD274: cluster of differentiation 274, CDC: complement-dependent cytotoxicity, CI: confidence interval, CLL: chronic lymphocytic leukemia, CR: complete response, CRC: colorectal cancers, CRS: cytokine release syndrome, CS: complement system, CTLA-4: cytotoxic t-lymphocyte-associated protein 4, CYP450: Cytochromes 450, DC: dendritic cells, DOR: duration of response, EFS: event-free survival, EGF: epidermal growth factor, EMA: European Medicines Agency, EpCAM: epithelial cell adhesion molecule, ET: epitope, antigenic determinant, Fab: antigen binding papain fragment of antibody, Fc: papain fragment crystallizable region of antibody, interacts with Fc-receptors, FDA: US Food and Drug Administration, FL: first-line treatment, GD2: a disialoganglioside, GM-CSF: granulocyte-macrophage colony stimulating factor, GVH: graft-versus-host, GVL: graft-versus-leukemia, GVT: graft-versus-tumor, Her2/neu: receptor tyrosine kinase erbB2, CD340 (EGF receptor family), HDs: Human diseases, HL: Hodgkin's Lymphoma, HSCs: hematopoietic stem cells, IL-6: Interleukin 6, M: million, mAb: monoclonal antibody, MAC: membrane attack complex, MCQC: molecular cell quality control, NHL: Non-Hodgkin's Lymphoma, NSCLC: non-small-cell lung carcinoma, nr: nor reached, ORR: objective response rate; also overall response rate, ORD, objective response duration, OS: overall survival, p: patient, PAP: prostatic acidic phosphatase, PD1: programmed cell death protein 1, PD-L1: programmed death-ligand 1, a protein encoded by the CD274 gene, PFS: Progression-free survival, PR: partial response, PT: paratope, AB-binding target interface, RANKL: receptor activator of nuclear factor kappa B-ligand, RCA: regulators of complement activation, SAE: severe adverse events, SLAMF7: slam family member 7, CD319 (marker or normal and malignant plasma cells), STS: soft tissue sarcoma, T: thousand, TGFα: transforming growth factor alpha, VEGF: vascular endothelial growth factor.

X. Declarations

a) Ethics approval and consent to participate

This manuscript is not a primary report on studies involving human participants, human tissue. It is only a review of the clinical trials in the field of cancer immunology and cancer immune-therapeutics.

b) Consent for publication

This manuscript does not contain any individual person's data in any form, including individual details, images or videos. A general consent for publication is given by the author of this work. An institutional consent form or any other person's consent form is thus not applicable.

c) Availability of data and materials

This manuscript cites the papers that were reviewed here and gives references also as a further reading material to the reader. For instance, several reviews were written before and are cited [1]–[9] but this new systematic review provides a holistic overview of may additional works that are cited too. If possible the doi and hyperlinks of the individual publications were also given to enable a fast access to the publications cited here in this work for all readers, which is often interesting for readers of a review. Further data sharing is not applicable to this article as no new primary datasets were generated than those that were already given in the publication, in the tables and references, or easily findable in the references herein. The corresponding author can also answer any further questions how to access the data, but references and websites are also very self-explicatory. Clinical trial information is incompletely accessible not due to the author's fault. Publicly available data were cited with a persistent identifier as required by BioMed Central.

d) Competing interests

There are no financial or non-financial competing interests added to the everywhere found persistent conflicts of interests to live and research in a crime controlled job market that is controlled by malicious networks that hinder normal postdoctoral careers in academia, in every firm, and in every sector. All sciences of today are biased from inherent conflicts of interest due to a systemic lack of independence.

e) Funding

There was no funding available for this work and the author never obtained fair chances in funding.

f) Authors' information (optional)

RA is an outstanding science, innovation, and business expert in biologics, biomedicine, life science, molecular biology, biochemistry, cell biology, and immunology. He also made accredited contributions to Harvard strategy, market research, intrapreneurship, drug discovery and biopharma-innovation.

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