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Highlights

Management of Senile Atopic

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Management of Senile Atopic Dermatitis in Geriatric Outpatient Clinic Dermatovenereology Department Ciptomangunkusumo Hospital in 2011-2015

By Lili Legiawati, Shannaz Nadia Yusharyahya & Marsha Bianti

Abstract- Background and objective: Senile atopic dermatitis is atopic dermatitis (AD) which persists until elderly or the onset first occur in elderly. Though it is relatively uncommon, the number of patients are gradually increasing in industrialized countries associated with aging society. The prevalence of senile AD remains unclear, and in Indonesia, there has not been any study regarding senile AD yet. Until now, there is no life-long cure for atopic dermatitis. Management comprises of treatment to protect the skin barrier, anti-inflammatory, and the identification and avoidance of trigger factors.

Method: This is a retrospective descriptive study. Secondary data was obtained from CiptoMangunkusumo Hospital medical record.

Result: In five year period, there were 54 senile AD patients with female predominance. Most patients were in 60-69 years old group (63%) and 31 of 54 patients were unemployed or already retired (57.4%). The most common type of onset was senile onset, which found in 45 patients (83.3%).

Keywords: geriatric, profile, senile atopic dermatitis, treatment.

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Method: This is a retrospective descriptive study. Secondary data was obtained from CiptoMangunkusumo Hospital medical record.

Result: In five year period, there were 54 senile AD patients with female predominance. Most patients were in 60-69 years old group (63%) and 31 of 54 patients were unemployed or already retired (57.4%). The most common type of onset was senile onset, which found in 45 patients (83.3%). Based on severity, most cases (58%) were classified as a moderate senile AD and treated with intermittent use of mid-potency topical corticosteroid, as well as regular application of emollient.

Conclusion: On observation, the number of senile AD cases are increasing along with the increasing number of geriatric population and it should not be underestimated. Proper management of senile AD may improve patients' quality of life.

Keywords: *geriatric, profile, senile atopic dermatitis, treatment.*

I. INTRODUCTION

Senile atopic dermatitis (AD) is a chronic relapsing skin disorder, which manifests as dry skin, itching, and various forms of eczematous inflammation which persists until elderly or with the first onset in elderly.¹ The number of cases is relatively small thus the prevalence data of senile AD remains limited until now. However, this number is increasing in industrialized countries.^{2,3} One study shows that the prevalence of AD in adult and elderly is 1 to 3%.⁴ Other shows the prevalence of AD in > 50 years old patients is 1.5 to 10%.⁵ However, in Indonesia, the prevalence of senile AD is not available yet.

Diagnosis and treatment of skin related diseases in elderly remain a challenge to dermatologists because of the atypical clinical manifestations due to aging skin. Geriatric patients also tend to have several health problems, altered body organ functions, and history of previous medications, which make diagnosing and treating skin-related diseases even more complicated. Therefore, a study regarding this topic in geriatric outpatient clinic Dermatovenereology Department CiptoMangunkusumo Hospital in 2011-2015 is needed to know the prevalence and patients' profile as well as the treatment of choice.

II. METHOD

This is a retrospective descriptive study, using secondary data obtained from CiptoMangunkusumo Hospital medical record. Data was taken from February 2016 until all was obtained. The subject were all patients, male and female ≥ 60 years old and clinically diagnosed as senile AD patients, who came to geriatric outpatient clinic dermatovenereology department CiptoMangunkusumo Hospital during 2011-2015. Those below 60 years old and with inactive medical record were exclude from this study.

The obtained data is then processed, analyzed, and critically appraised without statistical tests using IBM SPSS Statistic v.21. The data is described as socio-demographydata which consist of the year of visit, sex, age group, occupation, comorbidity, and history of atopy/allergy. The data are also described as special characteristics, such as the type of onset, severity, and treatment, then presented in tables and diagrams form with a narrative description.

III. RESULT

There were 54 cases of senile atopic dermatitis in geriatric outpatient clinic Dermatovenereology Department CiptoMangunkusumo Hospital during 2011-2015. Table 4.1 describes the sociodemographic characteristic of subjects.

Thirty-two of the 54 subjects (59.3%) are female and the rest, 40.7%, are male. Most patients belong in age group 60-69 years old (N=34, 63%). Thirty one of

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54 subjects are unemployed or already retired, 19 subjects are still doing domestic work as housewives, and only four still have active occupation.

Senile AD is classified into three groups based on the type of onset, which is senile onset, recurrent or continuation from adult form AD, and recurrent with

classical AD in childhood. In this study, majority of the cases were senile onset AD (N=45, 83.3%). Eight cases (14.8%) were continuation from adult form AD and only one case (1.9%) was a recurrent case with history of classic AD in childhood.

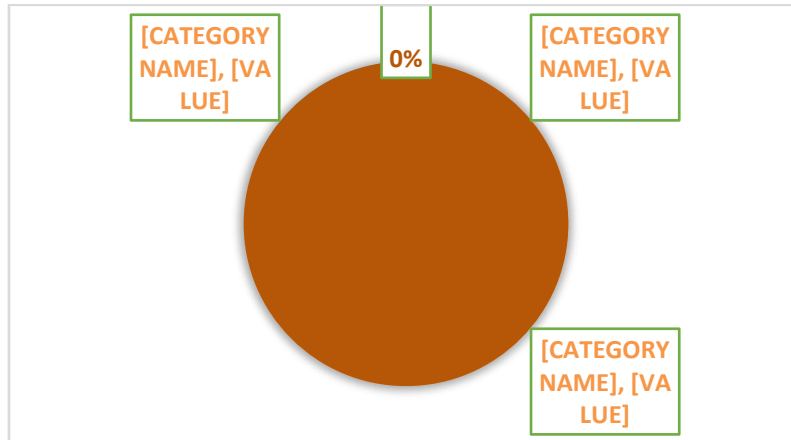


Image 4.1: Pie diagram showing senile AD type of onset percentage

Based on severity, most cases (58%) were classified as a moderate senile AD and treated with

intermittent use of mid-potency topical corticosteroid, as well as regular application of emollient.

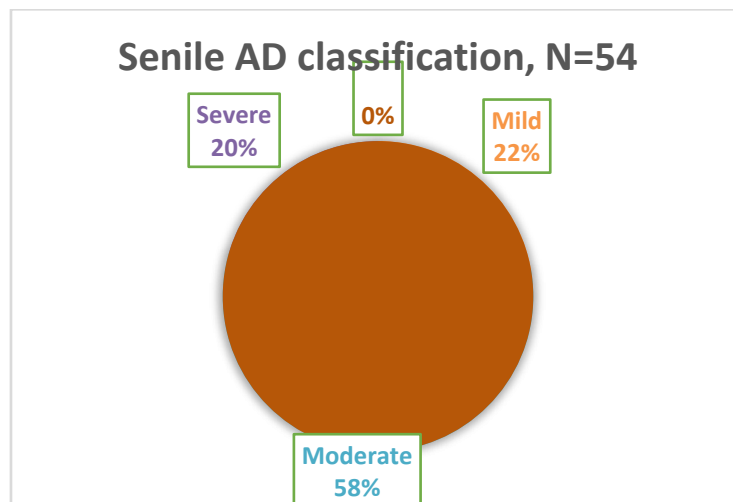


Image 4.2: Pie diagram showing senile AD classification based on severity percentage

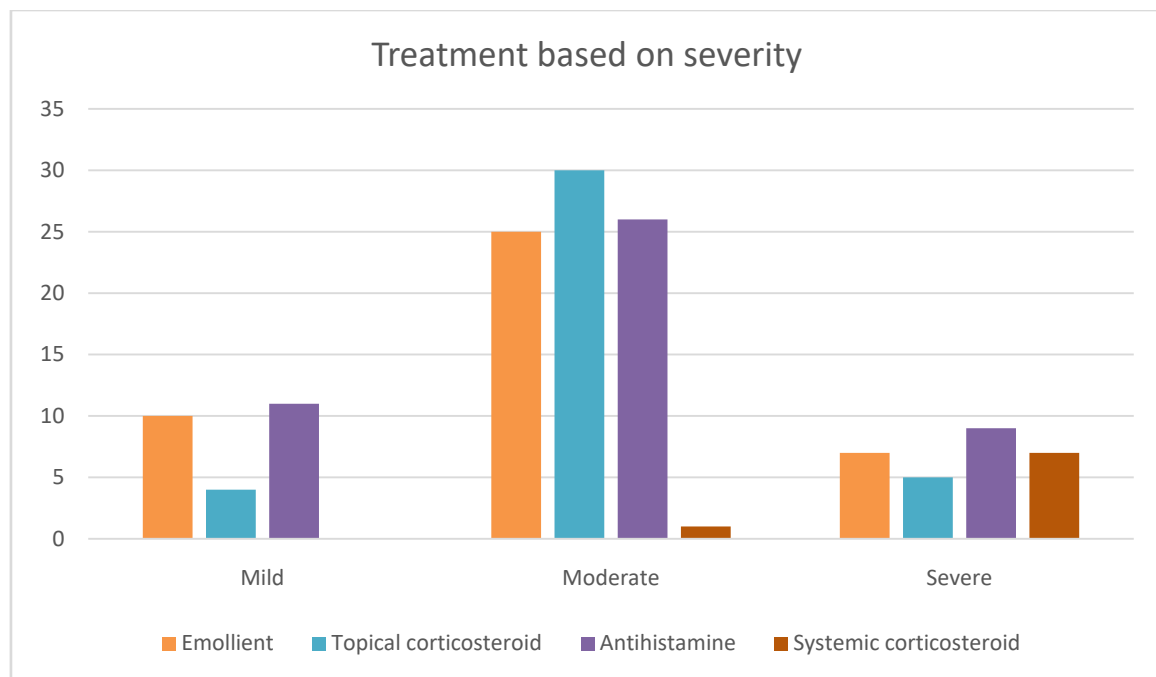


Image 4.3: Bar chart showing treatment of choice based on senile AD severity

IV. DISCUSSION

The subject of this study are all patients aged 60 years and older who came to geriatric outpatient clinic Dermatovenereology Department CiptoMangunkusumo Hospital and diagnosed with atopic dermatitis. The most common chief complaint is itch or pruritus. There were fifty-four patients in five years period, from January 2011 to December 2015. The most number of cases was recorded in 2012, as many as 20 cases (37%) and more than half of the total subjects belong to the age group 60-69 years old (N=34, 63%).

From the results, the number of female patients is more than male patients with almost 3:2 ratio. This result is different from Tanei⁶, which most senile AD patients found are male with 3:1 ratio to female. In other studies conducted in Japan, a male predominance was also found.⁷ In contrast, several studies of adult AD have indicated that the prevalence in women is higher than men.^{8,9} It is concluded that gender difference in the prevalence of senile AD is uncertain, our result probably because, in Indonesia, the number of female elderly is higher than male.¹⁰

The clinical findings of senile AD are basically similar to those in adult AD, except localized lichenification in the folds of the elbows and knees.¹ Variable and uncommon clinical findings of senile AD maybe due to individual differences in immune function, epithelial barrier function and environmental factors among elderly people associated with aging.⁶ In contrast to infantile or childhood AD, only 17 (31.5%) of the 54 subjects have history of atopy or allergy on him/herself or on the family.

There are three classification of senile AD based on the type of onset, which are senile onset, recurrent or continuation from adult AD, and recurrent with classical AD in childhood. In this study, majority of the cases were senile onset AD (N=45, 83.3%). Eight cases (14.8%) were continuation from adult AD and only one case (1.9%) was a recurrent case with history of classic AD in childhood. The recurrence rate of AD in the senile phase in patients with history of childhood AD is still unknown. One study from Sweden shows that AD persisted in 59 to 68% patients who had history of adult AD, however this was noted after 25 to 41 years of follow up.⁸

Up until now, there is no 100% life-long cure for AD.⁶ Regardless of age, the successful approach to the management of AD requires a combination of interventions and treatments. A tailor-made medicine for AD is needed to treat each patient with different conditions, especially the elderly. The treatment aims to identify and eliminate triggering factors, protect and improve the skin barrier, as well as anti-inflammatory measurements.^{1,6}

Intermittent use of topical corticosteroid, along with a regular application of moisturizers and emollients, have been the standard management of the disease. Similar to our study, in mild to moderate cases of senile AD, the treatment comprises of emollient and topical corticosteroids. Antihistamines were also used as the first choice in oral therapy. It can inhibit release of chemical mediators and the sedative effects could also effective for intense itching that causes sleep disturbance.⁶

In elderly, avoidance of environmental triggering factors is often considered difficult. Moreover, because of their decreased activity daily living with aging and

lifestyle, they failed to apply topical medication sufficiently. Therefore, systemic corticosteroid may be used for moderate to severe cases of senile AD with close monitoring of adverse events such as hypertension, gastric ulcer, cataract, osteoporosis, and diabetes mellitus.⁶

V. CONCLUSION

The number of geriatric population is increasing every year, so is the related disease, and AD should not be underestimated. The successful approach to the management of AD requires a combination of interventions and treatments. A tailor-made medicine for AD is needed to treat each patient with different conditions, especially in the elderly. The data obtained in this study can be used as information, as well as advice, both for clinicians and patients to improve the management of patients which may increase patient's quality of life. The result could also be used for further research on senile AD.

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APPENDIX 1

Table 4.1: Overview of the Sociodemographic Characteristics of Senile AD Patients in Geriatric Outpatient Clinic Dermatovenereology Department CiptoMangunkusumo Hospital in 2011-2015

Variables	N	%
Sex		
Male	22	40.7
Female	32	59.3
Age group		
60-69	34	63.0
70-79	13	24.1
80-89	5	9.3
>90	2	3.7
Occupation		
Retired/unemployed	31	57.4
Housewife	19	35.2
Entrepreneur/ employee	4	7.4
Comorbidities		
Present	40	74.1
Not present	14	25.9
History of atopy/ allergy		
Present	17	31.5
Not present	37	68.5



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Awareness and Perception towards the Utilization of Cervical Cancer Screening (CCS) Services among Nurses in a Teaching Hospital in Ibadan, Nigeria

By Akinpelu A.O, Agboola O.A & Umezurike E.T

University Ibadan

Abstract- Invasive cervical cancer is the second-most common cancer in women world-wide, 80% of these cases were discovered through records to be from developing countries although it can be readily detected in the premalignant phase, cervical cancer remains the second most common cancer in Nigeria and fifth in the United Kingdom. The objective of this study is to determine awareness and perception affecting utilization of cervical cancer screening services awareness, perception and factors affecting utilization of cervical cancer screening services among nurses in Adobo Maternity Teaching Hospital, Ibadan, Oyo State, Nigeria. The research was a descriptive and cross-sectional study conducted in Adobo Maternity Teaching Hospital Ibadan, Nigeria. The study showed a high level of perception 106 (59.9%) among the nurses within this study and the nurses that had positive perception only 8 (19.0%) had undergone cervical cancer screening in the past.

Keywords: nurses, cervical cancer, screening, awareness, perception.

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Their knowledge of cervical cancer was not poor; 97.7% of the respondents have heard of cervical cancer screening as a form of cervical cancer prevention and 168 (94.9%) are familiar with the age range (between 16-65 years old) that are eligible to go for CCS, only 128 (72.3%) were aware of modern day CCS equipment under Oyo state hospital management board facilities. However only 16 (9.0%) have worked in CCS unit and only 8 (4.5%) had privileged to attend refresher course training to enhance their knowledge of CCS practice. The findings of this study show that majority of the Nurses at Adobo Maternity Teaching Hospital though they are aware yet only few have undergone cervical cancer screening.

Keywords: nurses, cervical cancer, screening, awareness, perception.

1. INTRODUCTION

Invasive cervical cancer is the second-most common cancer in women world-wide, 80% of these cases were discovered through records to be from developing countries. Although it can be readily detected in the premalignant phase, cervical cancer

Remains the second most common cancer in Nigeria and fifth in the United Kingdom as opined by Ahmed, Sabot and Iris (2013).

According to United States Cancer Statistics (1999–2011) Cervical cancer was rated the leading cause of cancer death among women living in the United States however, the number of cervical cancer cases reported in the past 40 years and the number of deaths have decrease significantly. This reduction was related to the fact that many women got regular Pap test which enabled them has a pre-cancer detection before it turns to cancer. By 2011, about 12,109 women in the United States were diagnosed with cervical cancer while 4,092 women death was from cervical cancer. Internationally, cervical cancer has been regarded as the third most popular type of cancer among women asides breast and colorectal cancer this was reported by Al-Meer, as eel, Al- Khalid, Al-Kowari and Ismail (2009).

As a developing country, Nigeria is not spared of the cervical cancer public health problem; Olaniyi (2010) reported that cervical cancer is the commonest female cancer and is the leading cause of female death. This is observed to be secondary to late presentation at an advanced stage of the disease and which could be due to false reassurance associated with having no symptoms of disease.

Jamal, Bray, Centre, Farley and Ward (2011) are of the opinion that cervical cancers are a preventable disease through proper screening, treatment and follow up. However, it is a serious public health problem as it account for over 275,000 female deaths and approximately 529,000 new diagnoses each year were recorded in global cancer statistics The World Health Organization (WHO) also reported that cervical cancer is the most common cause of the female cancer globally (WHO, 2012).

Blair (2009) not only agree that early detection is a proven cost-effective intervention for cervical cancer control strategy but are also of the opinion that cervical cancer screening has its potentials to greatly reduce deaths occurring from cervical cancer. Guido (2008) however views it as a major challenge for developing

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countries where lack of resources limits coverage of the cervical cancer screening.

An assessment of women’s knowledge of cervical screening was considered important as up to 92% of those dying from this form of cancer have never been tested (Nacelle, 2009). It has been noted that some women lack the knowledge about prevention of cervical cancer tests and its indications. Many women do not have a clear understanding of the meaning of an abnormal smear or the concept of pre-cancerous changes and many believe that the purpose of the prevention of cervical cancer test is to detect cancer (Ackerson, 2010).

a) Objectives of the study

To determine awareness and perception affecting utilization of cervical cancer screening services awareness, perception and factors affecting utilization of cervical cancer screening services among nurses in Adobo Maternity Teaching Hospital, Ibadan, Oyo State, Nigeria.

b) Specific Objectives includes

- ◆ To assess level of awareness of cervical screening among Nurses in Adobo Maternity Teaching Hospital, Ibadan.
- ◆ To determine the perception of Nurses in Adobo Maternity Teaching Hospital on cervical cancer screening.

c) Research questions

1. What is the level of awareness of cervical cancer screening among Nurses in Adobo Maternity Teaching Hospital?
2. What is the perception of Nurses at Adeoyo Maternity Teaching Hospital on cervical cancer screening?

II. METHODOLOGY

a) Research design

This descriptive and cross-sectional study was aimed at assessing and documenting the awareness, perception and factors affecting utilization of cervical cancer screening among Nurses in a teaching Hospital in Ibadan, Oyo state, Nigeria. The study sought to understand the perception of this population about cervical cancer screening, awareness and factors affecting utilization of cervical cancer screening.

Setting of Study: The study was conducted in Adobo Maternity Teaching Hospital Ibadan, Nigeria.

Target population: The study populations are professional Nurses working at Adobo Maternity Teaching Hospital Ibadan of which majority are females and in their reproductive age. The professional nurses’ cadres ranged between staff nurse and chief nursing officer with total number over 204 nurses in the following units Administration department, Gynecology ward,

Labor room, Antenatal ward, Ante-natal clinic, Immunization, Family planning, Main & minor theatres, Post caesarian section ward, Life saving scheme, SCBU, Sexually transmitted infection, Causality, Tuberculosis clinic (TBL), Crèche, Health education unit, CHOPD, NHIS, CNO’s, Clinical instructor officer and Lying-in- ward.

Sampling procedure and sample: This is a descriptive and cross-sectional study aimed at assessing and documenting the awareness, perception and factors influencing cervical cancer screening among nurses working at Adobo Maternity Teaching Hospital using a validated structured questionnaire.

Sampling Techniques: Stratified, proportionate and simple random sampling techniques were adopted for the selection of the 180 nurses from a total of over 204 nurses from all cadres of nurses in the hospital. The sample is a subset of the total population which gives representation size of 88% of the total Nurses population will be used.

Sample size determination: The sample size formula for estimating proportions will be used to calculate the required sample size for this study.

$$n = \frac{Z^2 (up)}{d^2}$$

n= minimum sample size

d= desired precision of the estimate, set at 0.05 (level of accuracy desired/sampling error (tolerance error 5%)

z= standard normal deviate (set at 1.96 for 95% confidence level)

p=the proportion of the population having the characteristic being measure 87% (cited in Arulogun et al, 2012)

q=the proportion of the population that does not have the characteristics (1-p)

p = prevalence of awareness of cervical cancer screening among female Nurses in NnamdiAzikwe University Teaching Hospital, Knew, Nigeria = 87

Therefore, p is 0.87

$$q = 1 - 0.87 = 0.13$$

Substituting for the values in the formula,

$$n = \frac{1.96^2 \times 0.87 \times 0.13}{(0.05)^2}$$

$$n = \frac{3.8416 \times 0.87 \times 0.13}{0.0025} = 173.79$$

$$n = 173.79$$

Estimated Sample size = **180**.

$$10\% \text{ non-respondent} = 1 - \frac{10}{100} = 0.9 \text{ (used for pilot study} = 20)$$

100

b) Inclusion Criteria

All the Nurses that volunteer to participate in Adobo Maternity Teaching Hospital, Hemet, and Ibadan.

c) *Ethical Approval*

Ethical approval was sought and obtained from the Oyo State Ethical Approval Board before this research was carried out.

III. RESULTS

a) *Age distribution of respondents*

The age of the respondent ranged from 23 to 59 years; the median age \pm standard deviation was 40 ± 9.5 years.

b) *Research Question 1: What is the level of awareness of CCS among Nurses in Adeoyo Maternity Teaching Hospital?*

To provide answer to this question, the frequency counts and the percentages of respondents to the items in section B and D of the instrument were computed and the results represented in table 9 and figure 4.9.

More than half of the respondent are aware of the cervical cancer screening 97 (39.5 and 15.2= 54%).

c) *Discussion, Summary and Recommendation*

There is a high level of perception 106 (59.9%) had positive perception only 8 (19.0%) had undergone cervical cancer screening in the past. The Chi square $X^2 = 10.172$, degree of freedom (df) is 1 and P value is 0.002 thus the null hypothesis is rejected.

d) *What is the level of awareness of CCS among Nurses in Adobo Maternity Teaching Hospital?*

In order to determine their level of awareness the respondents were asked to define cervical cancer higher percentage of the Nurses could not define cervical cancer 103 (58.2%) while 74 (41.8%) were able to define it correctly. However, majority of the respondent 168 (94.9%) are familiar with the right age to have cervical cancer done. The respondents are also aware that the facilities where the test can be done 165 (93.2%)

Their knowledge of cervical cancer was not poor; 97.7% of the respondents have heard of cervical cancer screening as a form of cervical cancer prevention and 168 (94.9%) are familiar with the age range (between 16-65 years old) that are eligible to go for CCS, only 128 (72.3%) were aware of modern day CCS equipment under Oyo state hospital management board facilities. However only 16 (9.0%) have worked in CCS unit and only 8 (4.5%) had privileged to attend refresher course training to enhance their knowledge of CCS practice.

The knowledge of availability of various types of cervical cancer screening method was fair: 130 (73.4%) of the respondents are aware of Pap smear, 49 (27.7%) Human Papilloma virus test, 10 (5.6%) Cone biopsy test, 12 (6.8%) Liquid based cytology and 46 (26%) Visual inspection with acetic acid.

Although their knowledge of cervical cancer screening as a form of prevention of deadly disease such as cervical cancer was fair only 42 (23.7%) have undergone CCS and only 8 (4.5%) had done a repeat screening (screened twice).

In Arul gun's (2012) study respondents' pattern of utilization of cervical cancer screening (CCS) services that only 174 (34.6%) of the respondents had made use of cervical cancer screening services. However pattern of utilization showed that 80 (46.0%) had accessed CCS only once, 48(27.6%) twice, 15(8.6%) thrice and 31(17.8%) four or more times with the University College Hospital being the mostly patronized (85.6%).

Unlike Arul gun's study only few Nurses have had cervical cancer screening in the past (42, 23.7%) and less than have had a repeat test (8, 4.5 % had done it twice) however (132, 74.5%) perceived it as crucial to women's health.

The research revealed that the Nurses level of awareness is in significant in making an informed decision; Nurses have adequate information but are not health informed. It then become a concern how well can they be an advocate that women should go for cervical cancer screening when they have not fully utilized its benefits personally.

e) *What is the perception of Nurses at Adobo Maternity Teaching Hospital on cervical cancer screening?*

According to Table 11 which showed the perception of respondents towards CCS.

130 (74%) respondents are of the opinion that not all Nurses are well trained to conduct cervical cancer training. 128 (72.4%) claimed that cervical cancer screening is time consuming and that it is not easy to leave work to go for CCS 121 (62.7%). Majority 107 (60.4%) of the respondents claimed that CCS is a painful procedure and they cannot withstand the pain thus cannot go for it.

According to Kholo et al (2011) some women sometimes have their own perception about cervical cancer and the Pap smear, their study reveal that some women believe that women attend screening programs because they engaged in an active sexual lifestyle or contracted a sexually transmitted infection (STI). Because of this perception, many women do not attend for screening until the systems are well established and the condition is life threatening. Previous research also revealed that if women feel healthy, they feel no immediate need to attend for screening. This is similar to Kholo study only few of the respondents 25 (14.1%) perceived having multiple sexual partner as a possible risk for having cervical cancer. Majority of the respondents 168 (94.9%) disagreed that cervical cancer screening is for people of the lower class.

On accessibility Muppet (2011) study is of the opinion that proximity is a key factor to utilization, in her study with Zimbabwean women rural areas have limited

access to health centre providing CCS the respondents complained of distance being too far. Here the respondent working in a facility that has CCS service view its nearness to them positively 99(55.%) strongly agree to have the CCS done at their work place.

Respondents 132(74.5%) believes nurses see cervical cancer screening as crucial to women's health. 129(72.9%) disagreed that cervical cancer screening should be out of hospital – based services. Majority of the respondents 99 (55.9%) feels comfortable going for cervical cancer screening at their place of work.108(61%)respondents feels Hospital based cervical cancer screening services discourages Nurses .

The summary of group perception revealed that 106 (59.9%) among the one hundred and seventy seven Nurses at Adobo Maternity Teaching Hospital had a positive perception. Even though the general attitude is positive, 71 (40.1%) of the Nurses who have negative perceptions about cervical cancer screening needs to be targeted for re-orientation.

IV. CONCLUSION

The seriousness and hazards which cancer brings into the lives and existence of sufferers of the disease cannot be quantified. Cervical cancer is a type of cancer limited to and suffered by women and has serious adverse effect on the ability of women to function properly within their sphere as mothers, care givers and sometimes bread winners. Nurses due to their daily contact with patients, their relatives, friends and the general public can be viewed as fountains of knowledge. It is therefore important that they have the right kind of knowledge to disseminate information to the public

The findings of this study show that majority of the Nurses at Adobo Maternity Teaching Hospital though aware of cervical cancer, the availability and importance of screening, yet only few have undergone cervical cancer screening.

The Nurses' health promotion unit should also be resourced to handle promotional activities and programs through in-service trainings in providing informative education to help improve the level of awareness about cervical cancer screening among Nurses in general

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Tables and Figures for Awareness and Perception towards the Utilization of Cervical Cancer Screening (CCS Services among Nurses in a Teaching Hospital in Ibadan, Nigeria.

Table 1: Showing age grouping distribution of respondents

Age range (years)	Frequency	Percentage (%)
23-29	24	13.6
30-39	60	33.9
40-49	54	30.5
50-59	39	22.0
Total	177	100

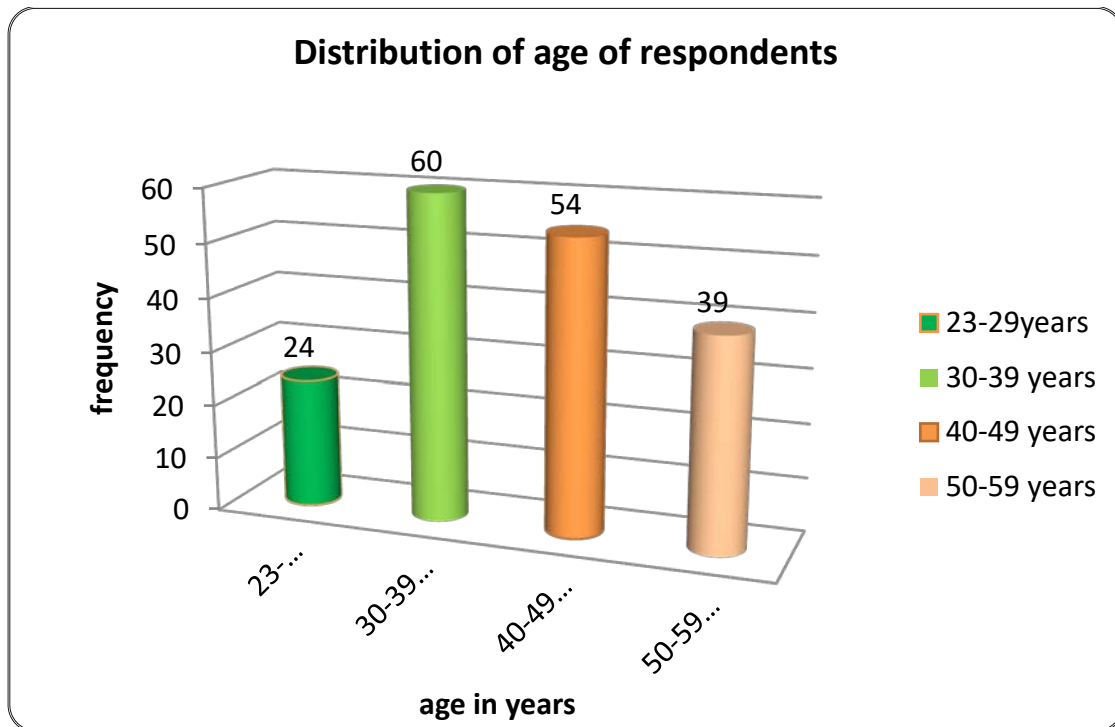


Figure 1: Bar Chart Showing Distribution of Respondents by Age

Table 2: Showing the Socio-demographic characteristics of respondents

S/N	Variables	Options	Frequency N=177	Percentage %
1	Age group			
		23-29 years	24	13.6
		30-39 years	60	33.9
		40-49 years	54	30.5
		50-59 years	39	22.0
2	Ethnic group			
		Igbo	6	3.4
		Yoruba	171	96.6
3	Marital status			
		Never married	12	6.8
		Married	157	88.7
		Widowed	8	4.5
4	Religion			
		Christianity	158	89.3
		Islam	19	10.7

5	Educational status			
		RN	19	10.7
		RN/RM	136	76.8
		B.Sc. nursing	16	9.0
		B.Sc.	6	3.4
6	Professional cadres			
		NO I	17	9.6
		NO II	44	24.9
		SNO	22	12.4
		PNO	52	29.4
		CNO	41	23.2
		ACNO	1	0.6
	Total		180	100%

Table 3: Showing distribution of respondents by marital status

Marital Status	Frequency	Percentage (%)
Never married	12	6.8
Married	157	88.7
Widowed	8	4.5
Total	177	100

Table 4: Showing frequency distribution of respondents' religion

Religion					
		Frequency	Percent %	Valid Percent %	Cumulative Percent %
Valid	Christianity	158	89.3	89.3	89.3
	Islam	19	10.7	10.7	100.0
	Total	177	100.0	100.0	

Table 5: Showing Educational status of respondents

Educational status					
		Frequency	Percent %	Valid Percent %	Cumulative Percent %
Valid	RN	19	10.7	10.7	10.7
	RN/RM	136	76.8	76.8	87.6
	B.Sc. nursing	16	9.0	9.0	96.6
	B.Sc.	6	3.4	3.4	100.0
	Total	177	100.0	100.0	



Table 6: Showing cadre distribution among respondents

Cadre					
		Frequency	Percent %	Valid Percent %	Cumulative Percent %
Valid	NO I	17	9.6	9.6	9.6
	NO II	44	24.9	24.9	34.5
	SNO	22	12.4	12.4	46.9
	PNO	52	29.4	29.4	76.3
	CNO	41	23.2	23.2	99.4
	ACNO	1	.6	.6	100.0
	Total	177	100.0	100.0	

Table 7: Showing distribution of areas of practice- duty post of valid respondents

Area of practice					
		Frequency	Percent %	Valid Percent %	Cumulative Percent %
Valid	Casualty	11	6.2	6.2	6.2
	Main theatre	2	1.1	1.1	7.3
	Labour room	41	23.2	23.2	30.5
	Antenatal ward I	13	7.3	7.3	37.9
	Antenatal war II	11	6.2	6.2	44.1
	Paediatrics	8	4.5	4.5	48.6
	SCBU	7	4.0	4.0	52.5
	Lying-in-wards I	19	10.7	10.7	63.3
	Lying-in-wards II	6	3.4	3.4	66.7
	CHOPD	6	3.4	3.4	70.1
	ANC	2	1.1	1.1	71.2
	Crèche	1	.6	.6	71.8
	Gynae/septic ward	4	2.3	2.3	74.0
	Family planning	3	1.7	1.7	75.7
	NHIS	1	.6	.6	76.3
	Gynaecological clinic	7	4.0	4.0	80.2
	Administrative Nurse	1	.6	.6	80.8
	Not disclosed	34	19.2	19.2	100.0
Total	177	100.0	100.0		



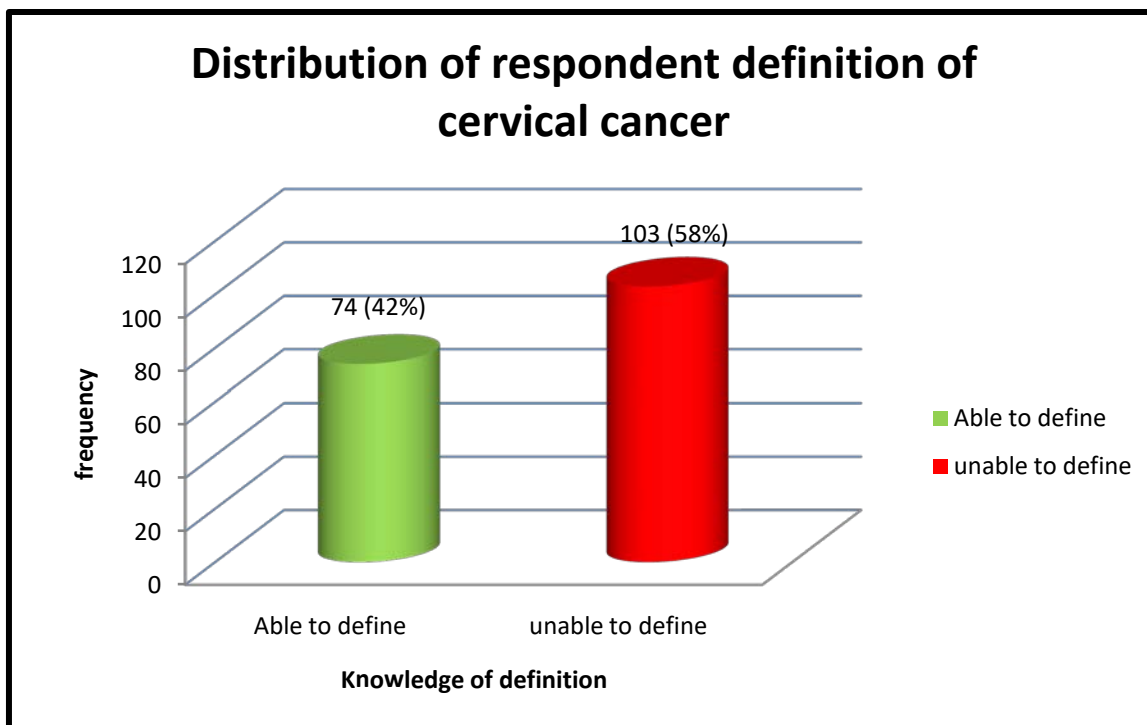


Figure 2: Bar chart showing respondents who are able to define cervical cancer correctly

Table 8: Showing Distribution of sources of awareness about CCS

Source of awareness	Frequency	Percent
Seminar	1	0.6
From friend	4	2.3
Not applicable	4	2.3
In media	12	6.8
During training	36	20.3
Read about it	120	67.8
Total	177	100.0

Table 9: Distribution of respondent awareness about cervical cancer screening

S/N	Items	Responses		Total N=177
		Positive	Negative	
1	What is cervical cancer?	74	103	177
2	Have you heard of CCS?	173	4	
3	Who is eligible to go for CCS?	168	9	
4	Is CCS available in your state?	165	12	
5	Are you aware of the modern day CCs equipment?	128	49	
6	Does Oyo state hospital management board have functioning modern CCS equipment?	173	104	
7	Have you worked in CCS unit before?	16	161	
8	Are you sent for CCS refresher course?	8	169	
9	Have you undergone CCS?	42	135	
10	What time during the menstrual cycle is the test best carried out?	50	127	
11	Is pap smear available?	130	47	
12	Is HPV available?	49	128	
13	Is cone biopsy available?	10	167	
14	Is Liquid based Cytology available?	12	165	
15	Is visual inspection with acetic acid available?	46	131	
16	Aware of facilities with CCS services	127	50	

Table 10: Showing awareness score percentage of respondents

Respondent	Frequency	Range of scores	Percentage %	Remark
Awareness score of respondent about cervical cancer screening	80	0-40	45.2 %	Poor awareness
	70	41-69	39.5 %	Average awareness
	27	70-100	15.2 %	Good awareness
Total	N=177		100 %	

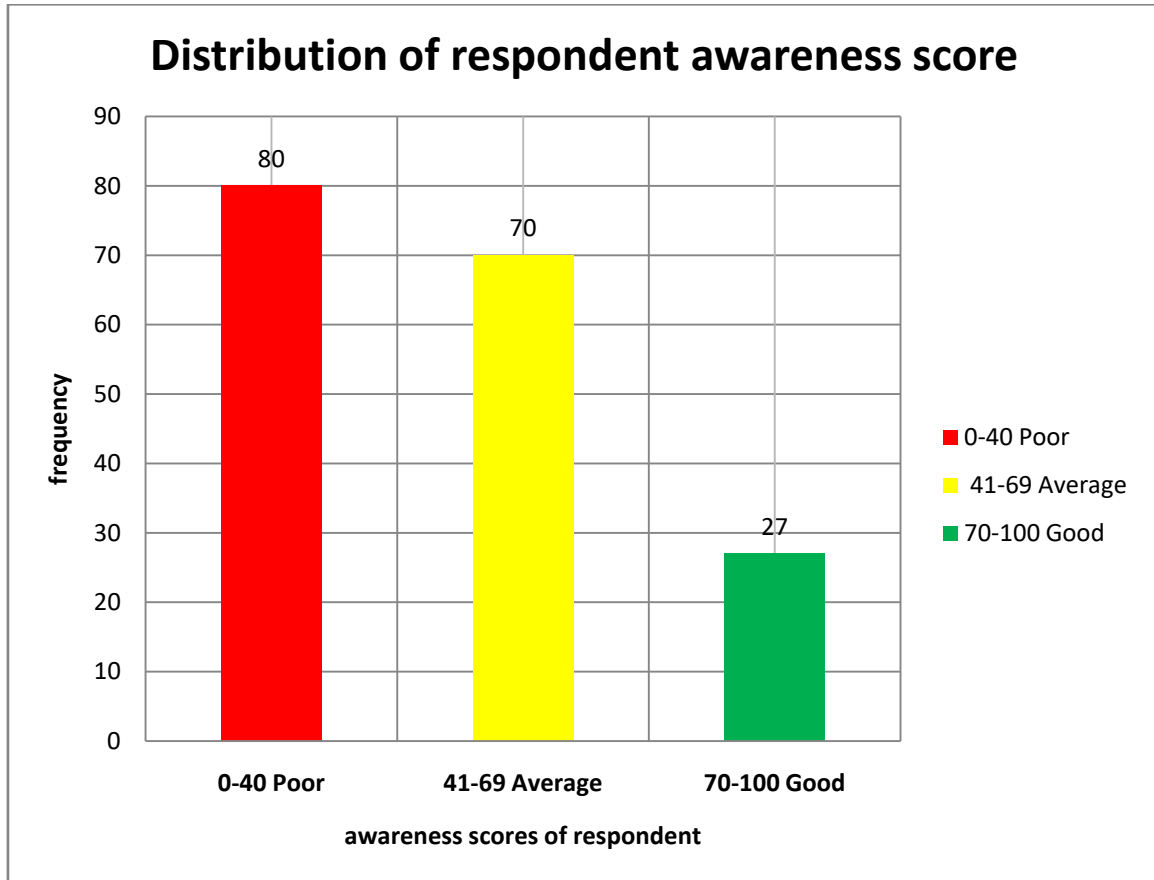


Figure 3: Bar chart distributions of respondents' awareness score

Research Question 2: What is the perception of Nurses at Adobo Maternity Teaching Hospital on cervical cancer screening?

Table 11: Showing perception respondents on CCS

S/N	ITEMS	Strongly Agree	Agree	Undecided	Disagree	Strongly Disagree
1	All Nurses are well trained to conduct cervical cancer screening.	5 (2.8%)	22 (12.4%)	19 (10.7%)	72 (40.7%)	59 (33.3%)
2	Cervical cancer screening is time consuming.	3 (1.7%)	15 (8.5%)	31 (17.5%)	81 (45.8%)	47 (26.6%)
3	It is not easy to leave work and go for cervical cancer screening.	9 (5.1%)	44 (24.9%)	13 (7.3%)	70 (39.5%)	41 (23.2%)
4	Cervical cancer screening is painful and I can't withstand the pain.	7 (4.0%)	22 (12.4%)	41 (23.2%)	76 (42.9%)	31 (17.5%)
5	I do not have multiple sexual partners, so I do not need cervical cancer screening.	6 (3.4%)	19 (10.7%)	10 (5.6%)	74 (41.8%)	68 (38.4%)

6	Cervical cancer screening is for people of lower social class.	2 (1.1%)	5 (2.8%)	2 (1.1%)	65 (36.7%)	103 (58.2%)
7	Nurses see cervical cancer screening as crucial to women's health.	62 (35.0%)	70 (39.5%)	12 (6.8%)	20 (11.3%)	13 (7.3%)
8	Cervical cancer screening should be out of hospital – based services.	8 (4.5%)	23 (13.0%)	17 (9.6%)	77 (43.5%)	52 (29.4%)
9	I feel comfortable to go for cervical cancer screening in my workplace.	26 (14.7%)	73 (41.2%)	24 (13.6%)	38 (21.5%)	16 (9.0%)
10	Hospital based cervical cancer screening services discourages Nurses.	16 (9.0%)	29 (16.4%)	24 (13.6%)	70 (39.5%)	38 (21.5%)

Test of Hypotesis

Null Hypothesis 1 (H₀1): There is no significant relationship between awareness and utilization of

cervical cancer screening among Nurses in Adeoyo Maternity Teaching Hospital.

Year 2018

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Table12: Summary of relationship between awareness of cervical screening and respondents who have undergone cervical cancer screening in the past

	User	Non-User	X ²	df	P-value	Remark	Decision
Aware	41 (97.6%)	132 (97.8%)	0.004	1	1	Insignificant	We fail to reject the H ₀
Not Aware	1 (2.4%)	3 (2.2%)					
	42 (100%)	135 (100%)					

Null Hypothesis (H₀ 2): There is no association between perception and utilization of cervical cancer screening

services among Nurses in Adobo Maternity Teaching Hospital, Ibadan.

Table 13: Perception summation group of positive and negative respondents

Perception summation group					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Negative perception	71	40.1	40.1	40.1
	Positive perception	106	59.9	59.9	100.0
	Total	177	100.0	100.0	

Table 14: Summary of respondent's relationship of perception summation group and Utilization CCS

	User	Non-User	X ²	do	Pave	Remark	Decision
Positive Perception	34 (81.0%)	72 (53.3%)	10.172	1	0.002	significant	We reject the H ₀
Negative Perception	8 (19.0%)	63 (46.7%)					
	42 (100%)	135 (100%)					



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Early Involvement by Extra-Pulmonary Sarcoidosis Presenting with Epigastric Pain

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Abstract- Gastrointestinal sarcoidosis leads to the formation of non-caseating granulomas in any GI-related organ. Overt presentation is rare, with subclinical involvement of the GI tract estimated to be higher. The diagnosis of GI sarcoidosis depends on clinical manifestations of the disease, and when possible, histology demonstrating characteristic non-caseating granulomas. Diseases capable of producing a similar clinical and/or histological picture must be excluded. Herein, we report a case of a patient with pulmonary sarcoidosis in remission, presenting with mild epigastric pain, and subsequently diagnosed with biopsy-proven gastric sarcoidosis.

Keywords: *sarcoidosis, GI sarcoidosis, extra-pulmonary sarcoidosis, gastrointestinal diseases.*

GJMR-F Classification: *NLMC Code: WG 269*



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Early Involvement by Extra-Pulmonary Sarcoidosis Presenting with Epigastric Pain

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& Edward Lebovics MD[‡]

Abstract- Gastrointestinal sarcoidosis leads to the formation of non-caseating granulomas in any GI-related organ. Overt presentation is rare, with subclinical involvement of the GI tract estimated to be higher. The diagnosis of GI sarcoidosis depends on clinical manifestations of the disease, and when possible, histology demonstrating characteristic non-caseating granulomas. Diseases capable of producing a similar clinical and/or histological picture must be excluded. Herein, we report a case of a patient with pulmonary sarcoidosis in remission, presenting with mild epigastric pain, and subsequently diagnosed with biopsy-proven gastric sarcoidosis.

Keywords: sarcoidosis, GI sarcoidosis, extra-pulmonary sarcoidosis, gastrointestinal diseases.

I. INTRODUCTION

Sarcoidosis is a well-known multisystem disease characterized by non-caseating granulomas.¹ Of those with extra-pulmonary involvement, the heart, lymphatic system, eyes and skin are the most frequently affected organ systems.² While gastrointestinal (GI) involvement is extremely rare with an incidence of <1%, the stomach remains the most common site of involvement.^{1,3} These cases of GI sarcoidosis are difficult to diagnose in that they are often clinically silent, and symptomatic in only 0.9% of patients.^{3,4,11}

II. CASE REPORT

A 41-year-old African American woman with known pulmonary sarcoidosis (in remission) presented to the ED complaining of epigastric pain for 5 days. She had previously been treated with prednisone, which was discontinued 8 years ago due to adverse side effects. She was doing well over the last several years off steroid treatment. However, over the last one-month prior to presentation, she did endorse a 10-lb weight loss, which she felt was "partly intentional," and ultimately presented due to the epigastric pain. She denies any nausea or vomiting.

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On encounter, the patient had normal vitals, with physical exam notable for mild epigastric tenderness on deep palpation, along with erythema nodosum of the lower extremities. There was no evidence of hepatic or splenic enlargement. Laboratory findings were significant for creatinine of 2.17 mg/dL, calcium 10.2 mg/dL, amylase 1583 U/L, lipase 89 U/L, alkaline phosphatase 171 U/L, C - reactive protein (CRP) 4.9 mg/dL, and angiotensin converting enzyme (ACE) 72 U/L.

A computed tomography (CT) scan of the abdomen showed no evidence of pancreatitis or gastric malignancy but highlighted the presence of retroperitoneal lymphadenopathy. Abdominal ultrasound with doppler revealed hepatic steatosis with no dilation of the bile ducts or cholelithiasis. Esophagogastroduodenoscopy (EGD) demonstrated moderate gastritis in the gastric body, antrum, and fundus, with no evidence of any ulceration or mass (Figure 1).

Multiple biopsies were taken from the stomach and normal appearing duodenum, which ultimately revealed focal ill-formed granulomas and few giant cells with calcified material (Figure 2). These findings, per expert review, were consistent with early involvement by sarcoidosis.

During the hospital course, the patient was given IV hydration and a daily oral proton pump inhibitor (PPI), with gradual improvement of her epigastric pain. Within 3 days, her creatinine normalized, suggesting a pre-renal cause of acute kidney injury, likely from poor appetite and dehydration. Given her overall improvement on a PPI and previous poor response to prednisone, the decision was made to hold off on steroid treatment. The patient's epigastric pain ultimately resolved and she was subsequently discharged on a PPI alone, with close follow up with gastroenterology.

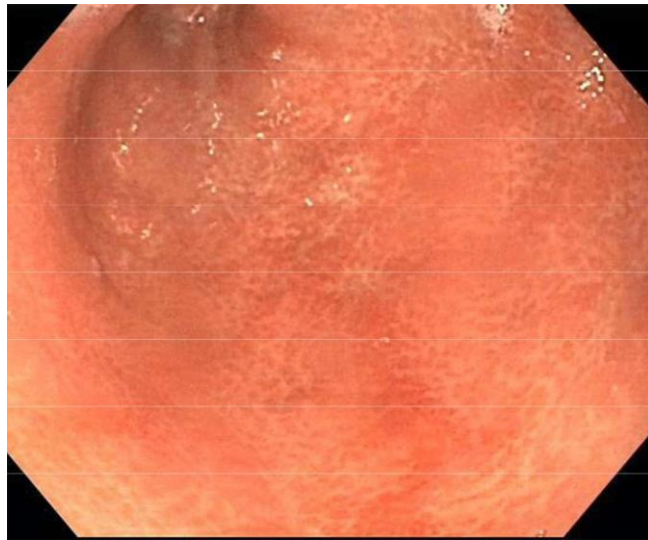


Figure 1: Esophagogastroduodenoscopy demonstrating gastric mucosa with mild erythematous changes

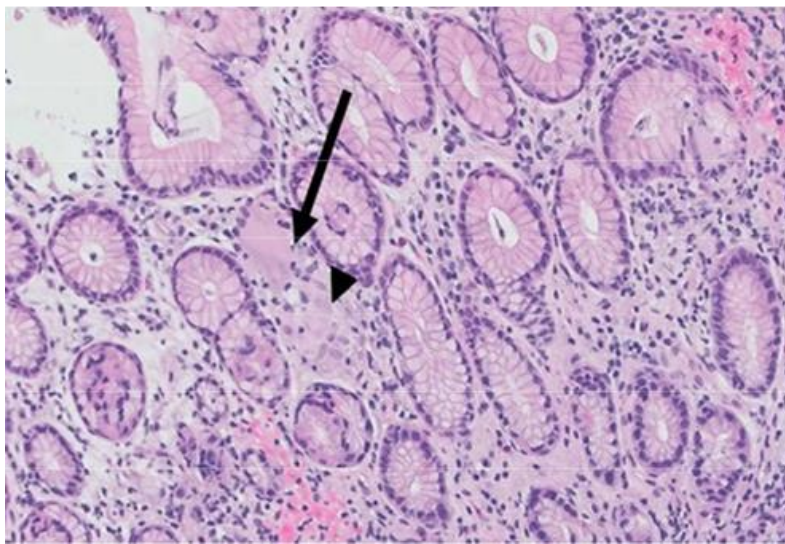


Figure 2: Gastric biopsy demonstrating fragments of gastric mucosa with mild chronic gastritis, focal ill-formed granulomas (arrow-head), and few giant cells (arrow)

III. DISCUSSION

Sarcoidosis is an inflammatory condition characterized by the formation of non-caseating granulomas in response to an unknown trigger.⁵ It most commonly involves the pulmonary system, however, non-pulmonary systems such as cardiac, gastrointestinal, reticulo-endothelial, ophthalmic, skin, and others, are commonly involved as well.^{6–8} African American women are the most frequently affected population, and have a higher incidence and prevalence of extra-pulmonary disease.^{9, 10, 12.}

Gastrointestinal disease is seen in only 0.9-1.1% of patients with sarcoidosis.^{1,3} The small bowel is the least common GI site affected by sarcoidosis, while the stomach remains the most common site of GI-tract involvement.^{3,11,13,14} These cases of gastrointestinal

sarcoidosis are often clinically silent. In those who are symptomatic, typical presentations include epigastric discomfort, and rarely, upper GI bleeding can be the presenting complaint.^{6,11,13,15,16} These findings were confirmed by Chinitz et al., in a review of 20 biopsy-proven cases of symptomatic gastric sarcoidosis.¹⁷ The most prominent symptom in these patients included epigastric pain in 75% and GI tract bleeding in 25%.¹⁷ Less common but well described presentation includes ulcers, polyps, or local/diffuse inflammation.¹⁸ They can also result in catastrophic outcomes, such as fibrosis leading to pyloric obstruction or the development of a neoplasm.^{7,13,15,19}

Diagnosis of gastric sarcoidosis is based upon the histologic evidence of non-caseating granulomas along with a compatible clinical history. The gastric mucosa on endoscopy can oftentimes appear normal;

hence, multiple biopsies and microscopic examination, has become essential for diagnosis.⁷ The microscopic appearance of gastric sarcoidosis varies from small aggregations of epithelial histiocytes with or without multinucleate giant cells to large nodular or polypoid aggregates of granulomas.¹⁹ Caution is necessary while arriving at a diagnosis of GI sarcoidosis solely on the basis of microscopic exam, as a collection of epithelioid cells may form as a reaction to non-specific agents.²⁰ Additionally, other granulomatous diseases, including Crohn's disease, Whipple's disease, reaction to malignancy, tuberculosis, histoplasmosis, and syphilis, need to be excluded as well.

Compared to sarcoidosis of the heart, nervous system and eye, where there is a clear role for corticosteroid use, the role of steroids in treating gastric sarcoid is less apparent.^{1,3,21} The decision to treat with steroids is largely based upon the severity of symptoms. In symptomatic patients steroids are the first line treatment of choice, and anti-acid therapy can be used as an alternative in less severe cases.^{13,18} Most patients respond well to steroids, and disease-modifying anti-rheumatic drugs are used for steroid refractory patients.⁷ Further studies are needed to fully assess the efficacy of corticosteroids in treating patients with GI sarcoidosis.

Given our patient's previous poor response to steroids, and her improvement in GI symptoms while on a PPI, we discharged our patient on a PPI alone. Whether she will need other immunosuppressive or surgical treatment will be based on the evolution of her symptoms on follow up.

Our case underscores the importance of considering gastrointestinal involvement of sarcoid in patients with a known history of sarcoidosis presenting with typical or unusual GI complaints. Individuals with organ-specific sarcoidosis, whether active or in remission, are still at risk for other organ manifestations of the disease. Clinical manifestations together with endoscopic biopsies remain pivotal for establishing a diagnosis, and allowing for appropriate directed management. Further studies are necessary to dictate standard treatment modalities for these patients with rare gastric manifestations of sarcoidosis.

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Blood Pressure Management in Frail Older People - The Real World Experience

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Abstract- According to recent evidence, blood pressure (BP) management benefits the same patients with mild frailty and fit subjects. In contrast, there is no evidence that antihypertensive treatment benefits patients with severe frailty, yet much evidence that such treatment is not safe. Notably, comorbidities can impact on benefits and harms of BP treatment. For enabling patient management based on individualized expected outcomes, there is a need to substantially increase observational data, focused on complex clinical situations and various comorbidities. In line with this aim, we present our experience from the perspective of longterm geriatric care. It is hoped that observations from the bedside, enhanced and expanded in the future, might contribute to the shift from empirical practice towards an evidence-balanced approach.

Keywords: arterial hypertension, elderly, frailty, hypotension.

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Blood Pressure Management in Frail Older People - The Real World Experience

Prof. Jochanan E. Naschitz, MD

Abstract- According to recent evidence, blood pressure (BP) management benefits the same patients with mild frailty and fit subjects. In contrast, there is no evidence that antihypertensive treatment benefits patients with severe frailty, yet much evidence that such treatment is not safe. Notably, comorbidities can impact on benefits and harms of BP treatment. For enabling patient management based on individualized expected outcomes, there is a need to substantially increase observational data, focused on complex clinical situations and various comorbidities. In line with this aim, we present our experience from the perspective of long-term geriatric care. It is hoped that observations from the bedside, enhanced and expanded in the future, might contribute to the shift from empirical practice towards an evidence-balanced approach.

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I. INTRODUCTION

Lowering the blood pressure (BP) in the elderly confers cardiovascular benefits, as was documented in SHEP, Syst-Eur, HYVET, and SPRINT (1-3). However, as shown in the regards cohort, in longstanding hypertension there may be a point of lesser return or no return. (4). With longstanding hypertension, this residual atherosclerotic damage becomes a prevailing risk factor, and hemodynamic normalization of BP confers less benefit (5). Guidelines of arterial hypertension treatment are not available for frail older people, but recent evidence indicates that BP management in patients with mild frailty should not differ from BP management in fit subjects (2). However, concerning patients with severe frailty there is no evidence that antihypertensive treatment reduces cardiovascular events, but much evidence that such treatment is not safe (6, 7). In recognizing that high BP in older adults is a complex and heterogeneous condition, the Report of the American College of Cardiology / American Heart Association Task Force on Clinical Practice Guidelines 2017 (8) makes a distinction between BP goals appropriate for fit patients and BP goals in hypertensive elderly subjects having a high burden of comorbidity and limited life expectancy. In the latter, clinical judgment and patient preference should be the basis of management. Indeed, achieving BP < 130 / 80 mm Hg may not be feasible in some older

patients (5). Not uncommonly, these patients experience dizziness and poor cognition when systolic BP hovers below 140 mm Hg. For now, over treated hypertension appears to be prevalent in nursing home patients.

a) Blood Pressure Measurement - Points Deserving Emphasis

Mercury sphygmomanometry has for long been the gold standard for BP measurement. However, mercury sphygmomanometers in the main have mostly been replaced with automatic devices. Oscillometric BP devices detect the motion of the BP cuff transmitted from the underlying artery, but the transmitted oscillations also depend on the arteries' stiffness and may be disturbed by low-frequency mechanical vibration originating in the environment. Oscillometric BP measurements may be patient dependent: hence, a disagreement between oscillometric BP and sphygmomanometric measurement may vary from patient to patient. Oscillometric BP measurements also are device dependent, because the algorithms used to compute the BP differ from one device to the other. An inconsistency of measurements by the same device and in the same patient may exist. A device passing a validation test does not mean that accurate readings in all patients will be achieved (9).

Clinic BP measurements alone to detect hypertension result in about 20% false-positive diagnoses due to the white-coat effect. The accuracy of office BP measurement can be improved by using a specially programmed electronic sphygmomanometer, capable of recording automatically, with the patient resting quietly and alone, an initial test reading followed by five additional readings at one or more minutes apart. There is evidence to support the replacement of manual office BP measurement with a such specially programmed automated BP device (e.g., the BpTRU), which is more accurate and not subject to a white coat response (10, 11). Twenty-four-hour ambulatory BP monitoring is the ideal method of diagnosing white-coat hypertension as well as masked hypertension. Concordance between office and ambulatory BP values is imperfect in nursing home residents, yet, this disparity appears to be unimportant in practice since one year survival of residents is predicted more accurately by disability than by BP (12). In long-term geriatric care, use of an automated BP device with multiple recordings on a single visit might serve as a more affordable alternative to 24-hour ambulatory BP monitoring (13).

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BP measurement may entail inaccuracies, some of which should be avoided: inappropriate cuff size; presence of arrhythmias causing the BP to be highly variable - multiple readings are needed to increase accuracy; unexposed inter-arm BP differences; missing the diagnosis of orthostatic hypotension when all measurements are obtained with the patient supine; missing the diagnosis of supine hypertension when all measurements are taken with the patient sitting; unawareness of hypotension during an acute febrile illness when medications need to be tapered down; BP overshoot after recovery from acute illness, when up-titration of antihypertensive medications may be required (14). Guidelines advise that the BP be measured on both arms, a recommendation often ignored. Measurement in only one arm may lead to underdiagnosis of hypertension. In practice, there should be awareness of the inherent limitations of automatic BP devices, of possible errors in measurement. Unlikely results need to be confirmed and interpreted within the clinical context, as illustrated by the following incident.

A 70-year-old woman was the first patient in a pilot study that aimed to assess the frequency of orthostatic hypotension (OH) and postprandial hypotension (PPH) in a population of severely frail patients. She was previously diagnosed with arterial hypertension and diabetes mellitus. Recently she suffered a minor stroke. At the time of admission for post-acute care, the patient's supine BP was 90-100/40 while being treated with three antihypertensive medications. Multiple BP measurements were recorded in the sitting patient with an automatic device by a physician, in conformity with the study protocol (Table 1). Along the measurements, the patient was awake and comfortable.

Table 1: Large Inter-Arm BP Difference, Unsuspected

Time	Relative to Lunch	Arm	SBP	DBP	HR
12.00	Before	Left	76	37	75
			76	43	72
			71	40	69
12.05		Right	115	48	72
			113	32	69
			117	48	70
13.05	After*	Right	128	53	72
			124	56	71
			120	55	71

*Lunch composition: total 480 Kcal, carbohydrates 250 Kcal, proteins 95 Kcal, lipids 135 Kcal

In recognizing a wide inter-arm BP difference in this patient, measurements were required to be done on the right arm (the arm with the higher BP): antihypertensive medications were titrated accordingly. This episode is a reminder to the recommendation, often ignored, that the BP should be measured on both

arms. The prevalence of systolic inter-arm difference of BP >10 mm Hg in the general population ranges from 14% to 23.6% and several reports show no association with age. An inter-arm SBP difference ≥10 mmHg is associated with increased cardiovascular risk and a difference ≥ 15 mm Hg with an increased cerebrovascular risk (15). Measurement in one arm only, by chance with the lower BP, may lead to underdiagnosis or under treatment of hypertension.

The method of BP measurement is particularly important when determining the patients' BP goal. However, proper BP assessment is time-consuming. The consequence of inappropriate BP measurement may be that many people, labeled as patients with hypertension, receive pharmacologic therapy that is unlikely to provide benefit but may cause adverse events.

b) Diagnosing Arterial Hypertension

Arterial hypertension has been defined as usual systolic BP ≥140 mmHg and/or usual diastolic BP ≥90 mmHg. Above these BP levels, the benefits of antihypertensive pharmacological treatment have been established in randomized placebo-controlled trials (16). So defined, arterial hypertension affects one-fourth of the adult population: by 75 years of age, almost 90% of the people will have hypertension. Typically, patients who develop hypertension before the age of 50 years have combined systolic and diastolic hypertension, in which the main hemodynamic alteration is vasoconstriction at the level of resistance arterioles. Most patients who develop hypertension after the age of 50 years have isolated systolic hypertension, the primary abnormality being decreased distensibility of the large conduit arteries. Yet, in the oldest old, declining systolic BP is common. The GERDA cohort study provided longitudinal data on participants aged 85, 90, and ≥95 years from 2000 to 2015. The mean change in systolic BP was by -12 mmHg (SD -25) and was explained by deteriorating general health (17).

More restrictive BP categories have been proposed in recent guidelines: normal BP <120/80 mmHg, elevated BP 120-129/<80 mmHg, stage 1 hypertension BP 130-139/80-89 mmHg, stage 2 hypertension BP >140/90 mmHg (8). The new guidelines focus on proper BP measurement and encourage home BP monitoring. Based on the SPRINT study as well as the new guidelines (8), more aggressive treatment goals are recommended in the highest-risk patients. Concerning older adults, it can be assumed that the vast majority have a 10-year ASCVD risk ≥10%, placing them in the high-risk category that requires initiation of antihypertensive drug therapy at BP ≥130/80 mm Hg. In practice, there are reservations concerning the application of the lower threshold for hypertension diagnosis. In many older persons treating hypertension to goal BP according to the new guidelines may be

problematic, in particular in patients with numerous comorbidities and severe frailty (18).

c) *Hypertension and Frailty - The Blood Pressure Paradox in the Oldest Old*

There is scarce information about the prevalence of arterial hypertension among frail elderly patients. A cross-sectional study conducted on 619 older adults at a university-based outpatient center evaluated the prevalence of hypertension in the robust, prefrail, and frail elderly. Hypertension was more prevalent in the frail (83%) and prefrail (72.5%) groups than among controls (51.7%). Hypertension, physical activity, the number of prescribed drugs, and the cognitive performance were significantly associated with frailty status (19). A study from South Korea (20) analyzed data of 4,352 adults aged ≥ 65 years, among them 62.0% had hypertension and 21.3% had pre-hypertension. Hypertension prevalence was higher in frail elderly (67.8%) than in pre-frail (60.8%) or robust elderly (49.2%). It was suggested that intensive control of hypertension could influence the trajectory of frailty (15): a hypothesis that needs more substantiation (19).

A cross-sectional study in four nursing homes included 480 longterm residents, all Caucasian (Naschitz JE et al., presented at the meeting of the Israel Hypertension Society). Their average age was 83.2 years, 56% were women, the average CSHA frailty index was 6.1. A requirement for being included in the study was the patients being clinically stable during the current month. Excluded were bedridden persons. Oscillometric measurements at the arm level were recorded with a standard automated BP cuff system, Welch Allyn Spot Vital Signs, San Diego, USA. This model achieved a British Hypertension Society grade A for both SBP DBP: it also met the criteria for the Advancement of Medical Instrumentation protocol. The medians of sitting BP measurements recorded during the current month were analyzed and related to the intensity of antihypertensive treatment. The SBP average was 124.9 (SD 12.4), SBP median 125 mmHg. The DBP average was 70.5 (SD 7.2), median DBP 70 mmHg. Fifty-three percent of the patients were not receiving BP-lowering medications. For those receiving antihypertensive medications (about 2/3 were taking ramipril 2.5 mg/day), the mean 'intensity of antihypertensive treatment' (21) was 0.6, i.e., low doses and unexpected good response. There were infrequent OH or orthostatic symptoms, as all subjects were symptom-free on sitting for 3-4 hours. All enjoyed daily 15-20 minutes of assisted walk.

In two subgroups, 39 fallers and 102 without a history of falls during the preceding six months, the sitting BP variability was computed based on all sitting BP measurements recorded during the preceding six months. The standard deviation (SD) of the BP values in each subject was used as a measure of BP variability. A low visit-to-visit BP variability was found in both

subgroups (SBP SD 8.9 mmHg and 8.9 mmHg, respectively) in comparison to other studies. In the PROSPER study of elderly at risk the SD of the SBP was 14.4 mmHg: in the ASCOT-BPLA study the visit-to-visit SD of the SBP was 10.66 mmHg in amlodipine treated patients and 13.4 mmHg in atenolol-treated patients: in ALHAT the values were SBP SD 10.6, 10.5, and 12.2 for participants randomized to chlorthalidone, amlodipine, and lisinopril (22-24).

Remarkable and contrary to expectation were the normal SBP, normal DBP and normal PP (or normalized on treatment) in a population of old persons, the 'favorable' BP variability, and the tolerance to orthostatic challenges of daily life. The interpretation of this data is speculative, but for could be attributed to the survivor effect similar to the decreased prevalence of cardiovascular disease observed in patients above 85 years. Indeed, it is reasonable to assume that patients who survived the longest were the least likely to be afflicted by these conditions (25). In expressing our surprise relative to the observed and being short of understanding, we used to call this phenomenon "the blood pressure paradox of the frail oldest old."

d) *BP Goals for Older Adults with a High Burden of Comorbidity and Limited Life Expectancy*

Patients with frequent falls, advanced cognitive impairment, multiple comorbidities and limited life expectancy may be at risk of adverse outcomes with intensive BP lowering. Evidence-based recommendations for BP management in the latter are not available since persons presenting any of these conditions were not included in large RCTs focused on hypertension treatment.

The "J-side" of BP lowering: Vital organs may respond differently to BP lowering. While decreasing the BP to the proposed target may reduce the incidence of stroke and end-stage renal disease, any protective effect on coronary events may be nil or even reverted with low BP. Caution is needed in patients with severe organ impairment, with a recent cardiovascular event and in the old, in whom vital organs may be more affected by under perfusion related to a treatment-induced BP fall (26,27). A diastolic BP level of less than 60 mm Hg should be avoided due to the potential for an increase in cardiovascular risk (28). Whether diastolic BP <70 mmHg along with high pulse pressure and OH are independent risk predictors for vascular events, and whether their association with frailty increases the risk needs to be addressed in further studies.

Injurious falls on antihypertensive treatment: In examining the relationship between antihypertensive therapy, the achieved BP, frailty indicators, and Medicare claims for injurious falls, it was shown that neither on-treatment BP nor the number of classes of antihypertensive medications used was associated with injurious falls: yet, having more than one frailty indicator

was associated with falls. Thus, fear of injurious falls should not be an obstacle in prescribing antihypertensive therapy when deemed necessary. Frailty, on the contrary, especially when multi-dimensional, constitute a warning sign (29, 30).

The optimum age-related SBP in the 75+ old that was predictive of the lowest cardiovascular and 10-year mortality has been observed in the systolic BP range 140-179 mmHg. It appears that a moderately elevated BP might be a favorable augur in those aged >80years (31). A possible explanation to this observation may be a disturbance of regulatory mechanisms involved in the perfusion of vital organs: so, an elevated BP might act as a compensatory mechanism in the oldest old to preserve organ perfusion and prevent organ damage.

Disordered cerebral blood flow autoregulation: Autoregulation of the cerebral blood flow is a protective mechanism that maintains flow at a relatively constant level despite fluctuations of arterial BP. In general, a brachial mean BP ≥ 60 mmHg is thought to afford an adequate cerebral blood flow. Cerebral blood flow autoregulation may be affected by a diversity of physiologic and pathological conditions (32-36): advanced age, endotheliopathy, hypertension, diabetes mellitus, heart failure, hypocapnia, alkalosis, sympathetic arousal, autonomic failure, early after head injury, acute ischemic stroke or sepsis. The cerebral flow reserve also depends on the presence of cerebral small and large artery disease. A focal decrease of cerebral flow may cause transient ischemic events, subcortical infarctions, cognitive decline, while a global decrease may cause presyncope or syncope.

Hypotension induced by medication, dehydration or sepsis may trigger ischemic cerebrovascular or coronary events (37-39).

Orthostatic hypotension (OH) and postprandial hypotension (PPH) are common disorders which accumulate with age. OH is defined as a sustained reduction of either systolic BP by ≥ 20 mmHg or diastolic BP by ≥ 10 mmHg within 3 minutes of standing or on passive head-up tilt to at least 600 (40). Some patients have 'delayed OH' that occurs beyond 3 minutes of standing. The prevalence of OH may be as high as 30-50 % among residents in long-term geriatric care (41,42). OH may concur with dizziness, falls and frailty, and has been regarded as a major cause of morbidity. Despite a large fall in BP, patients with OH often are asymptomatic, i.e., OH unawareness. The latter is explained by efficient regulation of the cerebral blood flow, so the cerebral blood flow does not change within a large range of the systemic BP. In patients with chronic OH, the tolerance to low BP may expand as low as systolic BP 70 mmHg (43). Symptom-free OH has been described in patients with dementia (44) and also in 75% of a population with autonomic failure (45). OH in older people has been considered an omen of death

(46), but adjusted for frailty OH's impact on mortality was not significant (47, 48).

Postprandial hypotension (PPH) is defined as a decrease in systolic BP of at least 20 mmHg within two hours after a meal (49). PPH, like OH, is thought to be a major cause of morbidity in older people (50). Nearly all older persons living in nursing homes experience some postprandial decrease in BP, usually not meeting criteria for diagnosing PPH. The possibility of PPH should be considered in patients with syncope, falls and dizziness that occur within two hours after a meal. For diagnosing PPH, experts recommend that the patient have both postprandial symptoms and a postprandial BP decrease. It is considered a good practice that symptomatic patients undergo ambulatory BP monitoring with analysis of breakfast and lunch hemodynamics (49). Alternatively, precisely timed small numbers of measurements may be valuable with monitoring the BP and symptoms for 2 hours after a meal since the nadir in BP can occur as late as 2 hours postprandially (51).

Three tests are widely used for the diagnosis of OH: the supine-to-standing orthostatic test, the supine-to-sitting, and the head-up tilt test.

The supine-to-standing orthostatic test is frequently used according to the following protocol: the patient's brachial BP is measured after 5-10 minutes of rest in the supine position: then the patient stands up and measurements are repeated while the patient stands motionless for 3-5 minutes with the cuffed arm supported at heart level. While standing, the patient is asked to report dizziness or light-headedness, with the examiner recording the symptoms' transience or persistence. The procedure is aborted for safety reasons if the BP drops precipitously or presyncope ensues. Patients with severe autonomic failure have an immediate drop in BP on standing and OH is easily diagnosed. On the other hand, there are individuals in whom the onset of hypotension on standing is delayed, and the diagnosis is missed using the short orthostatic test (52,53). The methodology of the supine-to-sitting orthostatic test is not standardized. One protocol often used involves a single BP measurement supine after prolonged recumbence followed by BP measurements after 1, 3 and 5 minutes of sitting. Other technical details are similar to those of the supine-to-standing test.

Reproducibility of cardiovascular responses on orthostatic challenge has been inconsistent (55, 55). OH was most prevalent and severe in the morning when subjects first arose: hence, OH may be underestimated when testing is performed in the afternoon (54). An influence of meals on the diurnal variation of OH has been observed.

e) *Screening Residents of Nursing Homes for OH and PPH Necessary?*

Frail older people have not been systematically assessed for OH and PPH. In a study from our

institution, we assessed BP changes related to posture and meals in frail older patients. The patient population comprised 50 older people, resident in long-term geriatric or hospice care, who were severely frail, ADL dependent, bed and chair confined, feeding orally. They were unfit to undergo standard postural and prandial tests, and unable to comply with ambulatory 24-hour-BP recording or beat-to-beat BP monitoring. The CSHA Clinical Frailty Scale (56) was used to estimate frailty severity, in which score 6 is the label for moderately frail persons needing help with both ADL and IADL and 7 indicates complete dependence. The average CSFA in the study population was 6.6 (SD 0.32). Excluded were patients not fully alert and those affected by an intercurrent illness such as febrile states, diarrhea, severe acute pain, exacerbation of dyspnea, and acute renal failure. The defining outcome of the study was postural fitness under real- life conditions rather than results of postural and prandial laboratory tests.

The brachial BP and HR were measured at heart level with a Spot Vital Signs® validated automatic oscillometric device. Supine BP and HR were recorded by a nurse at the bedside at 7 a.m.: for analysis, measurements taken over the previous ten days were used, including the measurement on the test day. Sitting BP and HR before lunch at 12 a.m. were measured on test day by a physician after the patients had been sitting in the dining room for 30-120 minutes. Three to five measurements were acquired, scrutinized for artifacts in real time, and discarded when found. Sitting BP and HR after lunch, in the dining room, at 12.40-13.00 a.m., were determined by the same physician. The medians of 3-5 measurements - supine, sitting before lunch and sitting after lunch - were chosen for analysis. Patient alertness and incident symptoms were assessed shortly before lunch and shortly after lunch. Incident symptoms were recorded, including dizziness, fatigue, lightheadedness, visual impairment, headache, chest pain, and pain in the shoulders or neck. Shortly after lunch, the patients were returned to their beds. Incident symptoms during the subsequent two hours were followed by nurses. Primary outcome measures of our study were the number of tests discontinued and incident symptoms occurring during the tests. Secondary outcome measures were incident OH (OH equivalent), incident PPH (PPH equivalent), and mean BP <60 mmHg at any time during the test. A BP drop to a magnitude, which on standard testing is diagnosed OH, by the present protocol was called 'OH equivalent.' We used the label 'PPH equivalent' to indicate a BP drop that under standard conditions (51) would be called PPH. The latter was correlated with the caloric content of the lunch consumed. The differences between supine BP and sitting before lunch BP were used to diagnose OH. Differences between sitting before lunch SBP and sitting after lunch SBP were used to diagnose PPH. During a four month period, 48 consecutive patients

fitting the inclusion criteria were evaluated once or twice. Their average age was 79.4 years (SD 10 years), with 22 males and 28 females. Results of measurements are shown in Tables 2 and 3. In no instance was the mean BP less than 60 mmHg. During a 2-16 months of hospitalization, there were neither falls, syncope, stroke, nor acute coronary events in the study population.

Table 2: Blood Pressure Measurements Supine and Sitting, Before and After Lunch

Parameter	Supine	Sitting Before Lunch	Sitting After Lunch
SBP mmHg, Mean (SD)	121.2 (16.8)	118.2 (19.1)	117.2 (20.9)
DBP mmHg, Mean (SD)	67.7 (10.5)	62.5 (10)	61.5 (9.9)
Heart Rate, Mean (SD)	80.8 (13.7)	76.8 (12.8)	79.6 (13.9)

Table 3: Number of Tests Exhibiting OH and PPH (Equivalents)

BP Change	Supine to Sitting Before Lunch	Sitting Before Lunch to Sitting After Lunch
A. SBP Decrease by ≥ 20 mmHg	9	8
B. DBP Decrease by ≥ 10 mmHg	16	4
A and / or B	23	8

In general, a brachial mean BP ≥ 60 mmHg (63/63 tests in the present study) is considered satisfactory to provide adequate cerebral blood flow. However, the situation may early after head injury or an acute ischemic stroke when autoregulation of the cerebral blood flow may be altered, and the brain remains unprotected against BP changes. Cerebral blood flow autoregulation may also be compromised during sepsis, potentially resulting in brain damage (36). No patient in our study belonged to either category mentioned above. In patients with severe frailty, there is no proof that diagnosis of asymptomatic OH and PPH improves the clinical outcomes (57,58). On the other hand, when symptoms of low cerebral perfusion occur, an appropriately elaborate work-up and treatment should be implemented.

The routine of residents sitting and eating in the dining room is always preferred to isolation and being bed-bound. In observing that severely frail older people tolerated the postural and prandial challenges to which they had been habitually exposed, the message could be that systematic screening residents for OH and PPH might be unnecessary and avoidable.

f) *Deintensification of Antihypertensive Treatment*

Little is known about deintensification of antihypertensive treatment in elderly hypertensives (59), in general, and so in the particular case of severely frail older people. A retrospective pilot study from a long-term comprehensive nursing institution addressed severely frail residents (Naschitz et al., unpublished observations). Included were 24 previously diagnosed hypertensives who were clinically stable for at least three months, not contracting any inter current disease. There were 13 males and 11 females: their mean age was 72.8 years (SD 14.9), their frailty severity 6 or 7 according to the CSHA Clinical Frailty Scale. The BP was recorded with a validated automatic BP device in supine position. Measurements obtained one month after admission, the time considered adequate for accommodation in the new surrounding, were compared with measurements obtained 3 months later. The median of all readings, 5 or more, obtained over 10-14 days was calculated for each of the two time periods. The number of different antihypertensive medications was counted and the intensity of antihypertensive treatment was calculated for each period (21). In being a retrospective analysis, adjustments of treatment were done in conformity with common practice and were not motivated by the principle of deintensification. The patients' BP data in relation to antihypertensive treatment is shown in Table 4.

Table 4: Blood Pressure Relative to Antihypertensive Treatment

	Admission	Three Months Later
Supine BP, mmHg (Median)	123 / 74	121 / 69
No Patients on Anti-HT Medications	13 / 24	11 / 24
No of Anti-HT Drugs (Median)	3	1
Intensity of Anti-HT Treatment (Median)	1	0.5

Eleven out of 24 patients with a history of arterial hypertension had on admission normal BP without receiving antihypertensive medications. In one patient antihypertensives were discontinued: the BP remained within the normal range. In patients continuing to receive antihypertensive medications the dose and number of antihypertensive medications were reduced to get at goal BP (except one patient). Tapering antihypertensive treatment was unrelated to use of high dose opiate, sedative medications, inter current illness, dehydration, or end-stage cancer. Deintensification of antihypertensive treatment did not cause an overshoot of BP or any adverse event. A possible benefit of medication deintensification, as expected on theoretical grounds, could not be attested in the absence of a

comparator cohort group, though adverse effects of low BP might have been avoided.

g) *Where Evidence is Scarce*

Evidence-based medicine encourages the following of defined care pathways. Such evidence is evolving in patients with mild frailty but is not existing in patients with severe frailty and multimorbidity. Notably, comorbidities impact on benefits and harms of treatment (60-62). To enable physician decision making based on individualized expected outcomes, there is need to collect data focused at defined clinical categories, i.e., one or several chronic diseases in addition to advanced age and frailty (60-62). Observations from the bedside, enhanced and expanded, might contribute to a shift from empirical practice towards an evidence-balanced approach (61).

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Non Functioning Paraganglioma of the Urinary Bladder Treated by Transurethral Resection: Report of a New Case

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Abstract- Paragangliomas are extra-adrenal tumors of the autonomic nervous system and may be found within the skull base, neck, mediastinum and periaortic region. Paragangliomas of the urinary bladder are rare, and nonfunctioning bladder paraganglioma is even rarer and not easily recognized. Histological examination is often key in leading to a definitive diagnosis. The current report presents a case of a 59-year-old female with urinary bladder paraganglioma. The patient presented with only painless gross haematuria. A transitional cell carcinoma was suspected, but histological examination and immunohistochemistry of a transurethral resection specimen confirmed the correct diagnosis. In the present report, the clinical features, diagnosis, and management of nonfunctional paraganglioma of the urinary bladder are discussed.

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NONFUNCTIONINGPARAGANGLIOMAGFTHEURINARYBLADDERREATEDBYTRANSURETHRALRESECTIONREPORTOFANEWCASE

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Non Functioning Paraganglioma of the Urinary Bladder Treated by Transurethral Resection: Report of a New Case

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Abstract- Paragangliomas are extra-adrenal tumors of the autonomic nervous system and may be found within the skull base, neck, mediastinum and periaortic region. Paragangliomas of the urinary bladder are rare, and nonfunctioning bladder paraganglioma is even rarer and not easily recognized. Histological examination is often key in leading to a definitive diagnosis. The current report presents a case of a 59-year-old female with urinary bladder paraganglioma. The patient presented with only painless gross haematuria. A transitional cell carcinoma was suspected, but histological examination and immunohistochemistry of a transurethral resection specimen confirmed the correct diagnosis. In the present report, the clinical features, diagnosis, and management of nonfunctional paraganglioma of the urinary bladder are discussed.

I. INTRODUCTION

Paraganglioma of the urinary bladder is a rare tumor, accounting for less than 0.06% of all vesical tumors and less than 1% of all the pheochromocytomas [1, 2]. About 98% of the paragangliomas are located in the abdomen, 90% of these are in the adrenal medulla with 10% extra-adrenal sites extending from neck to the pelvis [3]. Paraganglioma arises from the chromaffin tissue of the sympathetic nerves of the bladder wall. As they are rare tumors there are pitfalls in their diagnosis, and no standard treatment protocols are available.

II. CASE REPORT

A 59-year-old woman complaining of painless gross hematuria for six months was admitted to our hospital. Her family history was unremarkable, and she had no previous medical problems. Her blood pressure was 110-130/70-80 mmHg, and her heart rate was in the normal range. Physical examination showed no evidence of hypertensive disease. Abdominal ultrasound showed a large protruding tumor over the left lateral wall of the bladder measuring 4.0 × 3.0 cm (Figure 1). Our patient underwent a cystoscopic examination, and a

submucosal mass was seen on the left lateral wall near the neck of the urinary bladder, with normal mucosal covering. No sign of any metastatic disease was found on computed tomography (CT) scan of other abdominal organ systems.

Transurethral resection of bladder tumor (TURBT) was performed (Figure 2). This TURBT was complete, and tissue was submitted for histopathological examination.

Histologically, bladder mucosa was infiltrated by a proliferation arranged in nests and lobules which are surrounded by a thin vascular network (Figure 3). Tumor cells were polygonal, and provided with an abundant amount of granular, eosinophilic or clear cytoplasm. The nucleus was round with delicate chromatin and inconspicuous nucleoli. There were no mitotic figures. Immunohistochemistry showed strong cytoplasmic positivity of chromogranin and synaptophysin (Figure 4). PS100 stained sustentacular cells and Cytokeratin was negative.

The final diagnosis was nonfunctioning paraganglioma of the urinary bladder. The Patient did not receive any further treatment. The Biopsy of the tumor bed during the first endoscopic control did not show any macroscopic or microscopic recurrence, and the rate of plasma free metanephrines was normal. On a recent follow-up at 24 months, her cystoscopy examination did not reveal any evidence of recurrence (Figure 3). Her radiological assessment (thoracic-abdominopelvic CT) was negative for metastatic disease.



Fig. 1: Ultrasound Examination Was Showing a Heterogeneous Mass in the Urinary Bladder Measuring 4.0 × 3.0 cm.

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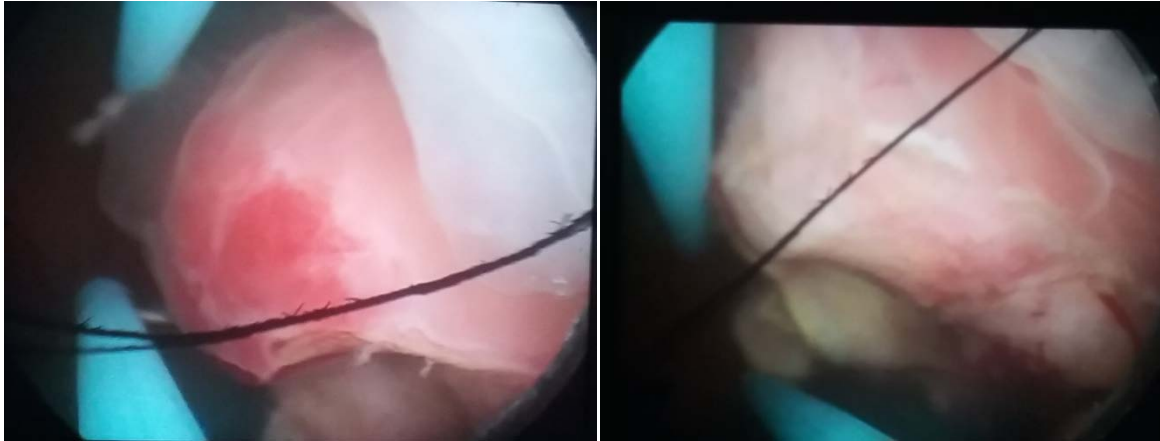


Fig. 2: Transurethral Resection of a Submucosal Bladder Tumor with Normal Mucosal Covering.

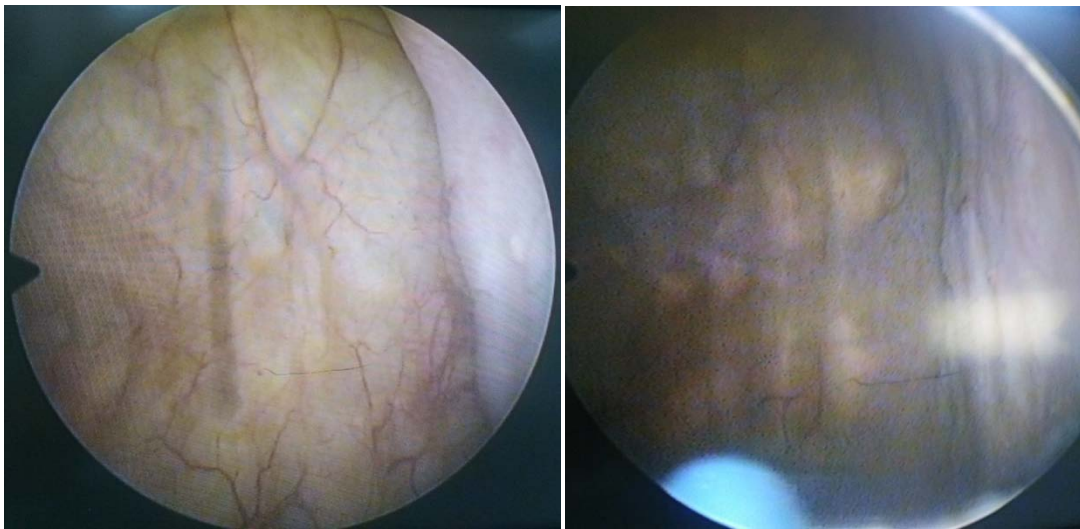


Fig. 3: First Cystoscopy After TURBT: No Tumor Recurrence. A Biopsy of the Tumor Bed was done.

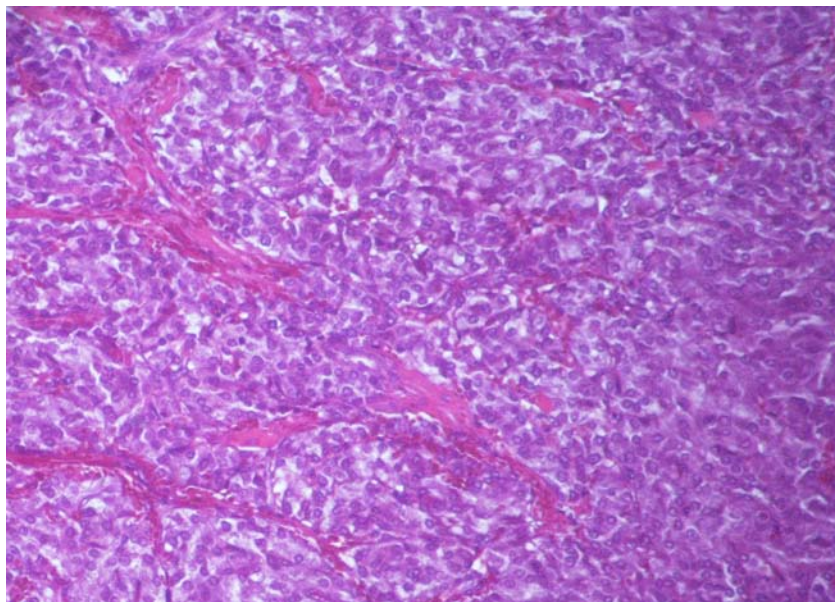


Fig. 4: (HEX10) Nesting, a Trabecular Proliferation of Polygonal Cells within a Vascular Network.

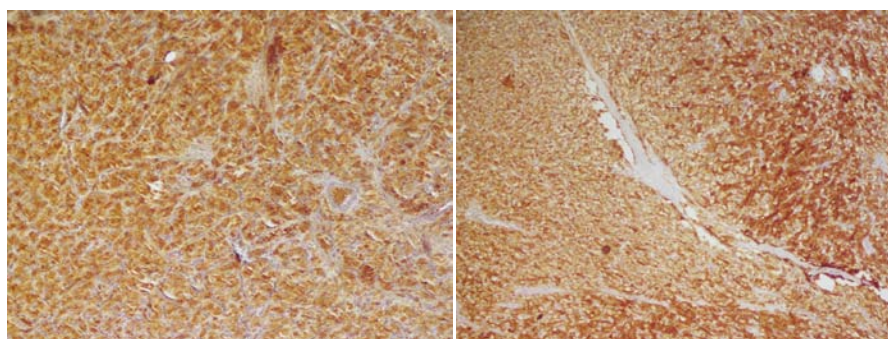


Fig. 5: Tumor Cells are Strongly Stained with Neuroendocrine Markers : Chromogranin (Left), Synaptophysin (Right).

III. DISCUSSION

Paragangliomas are tumors of the paraganglion system arising from chromaffin cells in or about sympathetic ganglia and account for 10% of all pheochromocytomas [4]. They account for < 1% of all bladder tumors [4].

Paraganglioma of the urinary bladder is rarely encountered, and nonfunctioning bladder paraganglioma is even rarer [5]. The first case of bladder paraganglioma was reported in 1953 by Zimmerman et al. [6].

The underlying mechanism of bladder paraganglioma remains unclear. Previous studies have shown that bladder paraganglioma occurs more frequently in females than males (female/male ratio is 3:1), primarily during the second and third decades of life [7]. The majority (83%) of paragangliomas of the urinary bladder are hormonally active [8]. However, nonfunctioning paragangliomas are rarer and more difficult to diagnose due to their nonsecreting nature [8]. Therefore, the patients provided no history of hypertension, headache or flushing that would suggest a diagnosis of secreting paraganglioma and endocrine tests, including catecholamines and vanillylmandelic acid in a 24-h urine sample, are rarely considered in the management of nonfunctioning paragangliomas [5].

Nonfunctioning bladder paragangliomas are often found in routine imaging exams that show the possibility of bladder cancer. In most methods of imaging, this neoplasm is indistinguishable from other types of tumors, but some features may lead to the suspicion of bladder paraganglioma such as small intramural lesions which may be accentuated after the administration of contrast in MRI, whereas larger lesions lose the uniformity of attenuation due to necrotic areas [9]. The signal strength on T2 weighted images can be very high in these tumors allowing their characterization [9]. The metaiodobenzylguanidine (MIBG) is highly specific for pheochromocytoma, and it can be useful to distinguish between functional and nonfunctional tumors, but it is less sensitive compared to MRI to detect paragangliomas [9, 10].

Determination of the site of primary or metastatic disease is probably best achieved with I-

MIBG scintigraphy when available. Its disadvantages include limited availability and high cost, reasons why our patient did not do it [11].

The cystoscopic appearance of a submucosal tumor, yellow at the cut, should raise the suspicion of bladder paraganglioma [12, 13]. Histopathologically, the tumor cells show characteristic zellballen or nesting pattern with delicate fibrovascular stroma [14]. Immunohistochemistry shows strong cytoplasmic expression of chromogranin, synaptophysin and neuron-specific-enolase in the tumor cells and supporting cells stain by S-100 protein [15]. The differential diagnoses of the urinary bladder paraganglioma include urothelial carcinoma, metastatic renal cell carcinoma, prostatic carcinoma, malignant melanoma, and granular cell tumor [14]. Histological appearance and immunoprofile as described above helped us to distinguish bladder paraganglioma from other differential diagnoses.

Between 5 and 15% of the paragangliomas of the urinary bladder are said to be malignant. However, no histological criteria have been established to distinguish between benign and malignant tumors. Only the appearance of local invasion or distant metastases confirms that the tumor is cancerous [16].

Treatment modalities include transurethral resection and partial or total cystectomy combined with pelvic lymph node dissection, especially in the presence of proven metastasis [17, 18].

With the advances in laparoscopy techniques, laparoscopic partial cystectomy has become the treatment of choice [5, 18]. However, the optimal management mode is still uncertain [5]. Transurethral resection is considered to be feasible in tumors of less than 3 cm in size without deep parietal infiltration [19]. In the present case, a transurethral resection was successfully performed, and we did not notice any transient hypertensive crisis during tumor manipulation. Our Patient did not receive any further treatment, and her cystoscopy examination and radiological assessment did not reveal any evidence of recurrence after a follow-up of 2 years.

However, regular follow-up is necessary to detect late recurrences [20]. It must be lifelong and



include cystoscopy and imaging study. No consensus has been established for the frequency of these measures: nevertheless, we suggested at least an annual follow-up for those patients who are asymptomatic or whenever clinically indicated.

IV. CONCLUSION

Non-functioning bladder paragangliomas may present clinical, radiology and pathological features similar to bladder cancer.

A definitive diagnosis may be reached only by histology, and no histological criteria have been established to distinguish between benign and malignant tumors.

Transurethral resection for bladder paraganglioma may be a treatment of choice, offering several advantages, including reduced invasion, rapid recovery and early discharge from the hospital, but the optimal management mode remains uncertain.

Long-term follow-up is recommended in all paragangliomas.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Advances in Cancer Immunology and Immunotherapy

By Roman Anton

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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.

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

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ADVANCES IN CANCER IMMUNOLOGY AND IMMUNOTHERAPY

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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 immunotherapeutics 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:

$$\text{Dependence } R_{x,y} = \frac{\sum_{i=1}^n (x_i - \bar{x})(y_i - \bar{y})}{\sqrt{\sum_{i=1}^n (x_i - \bar{x})^2} \sqrt{\sum_{i=1}^n (y_i - \bar{y})^2}} \quad \bar{x} = \frac{1}{n} \sum_{i=1}^n x_i \quad \text{and} \quad \bar{y} = \frac{1}{n} \sum_{i=1}^n y_i$$

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III. ADVANCES IN CANCER IMMUNOTHERAPEUTICS 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.

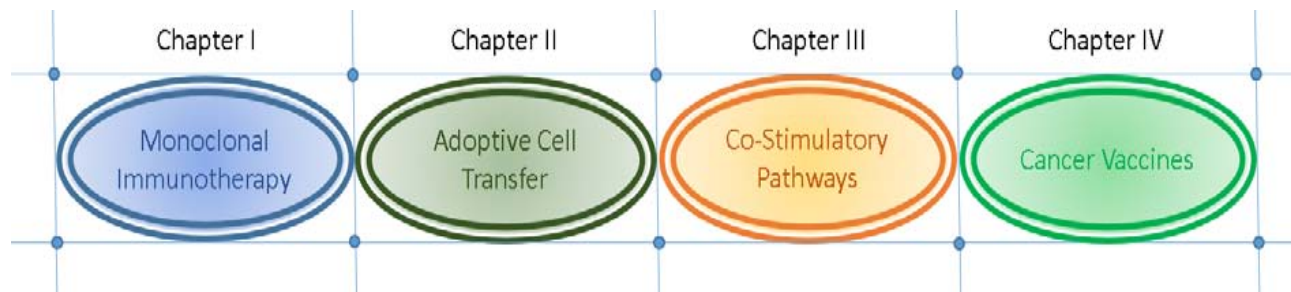


Figure 1: The Four Types of Cancer Immunotherapy in Four Nutshells: Review Chapter I - IV

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 success 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 assume, 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 prevailing thinking in biopharma 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 +/-131	GSK, Corixa	CD20	mouse IgG2a	2003	2003	Hybridoma	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
Erbix®	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® Perjeta®	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
Blinicyto®	Blinatumomab	Amgen, Micromet Inc.	CD19/CD3 engager	mouse	2014	2015	CHO	Philadelphia Chr. Neg. ALL	0,2 bn by 2023	43
Keytruda®	Pembrolizumab	Merck & Co	PD-1	human IgG4/k	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/k	2014	2014	CHO	Neoplastic Cancers; other	1,0 bn by 2023	24
Darzalex®	Daratumumab	Janssen Cilag	CD38	human IgG1/k	2015	2016	CHO	Multiple Myeloma	4,2 bn by 2022	78
Empliciti	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 Therapeutics Europe	GD2	human IgG1/k	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/k	2017	2017	CHO	NSCLC, Solid Tumors, diverse	2,2 bn by 2022	98
Imfinzi®	Durvalumab	AstraZeneca UK	PD-L1	human IgG1/k	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 to 2246

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 portfolios (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.

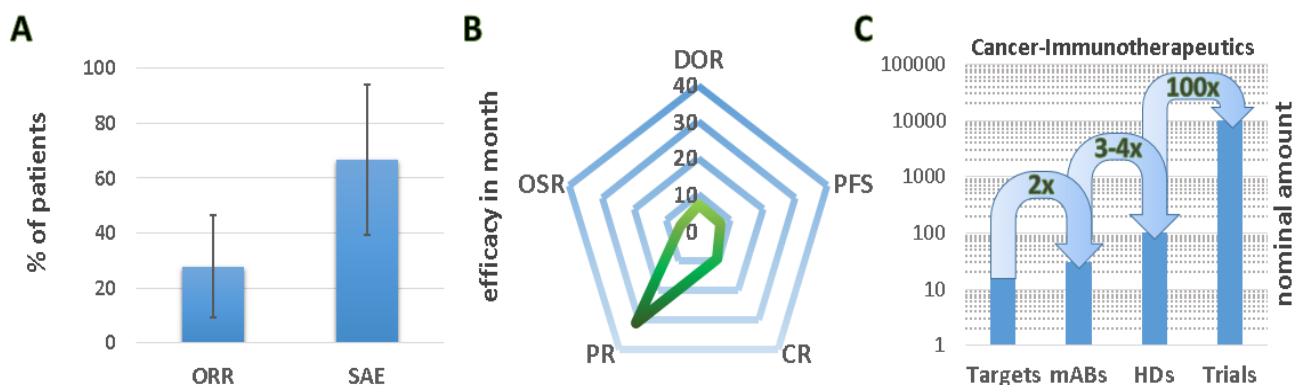


Figure 2: Cancer Immunotherapeutics, overall statistics of simplified rough estimates of clinical trials; ORR: Objective Response Rate (also: Overall Response Rate), SAE: Serious Adverse Events; DOR: Duration of Response (this is the duration of the ORR), PFS: Progression-Free Survival, CR: Complete 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-therapeutics while not so much attacking the host tissues 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.

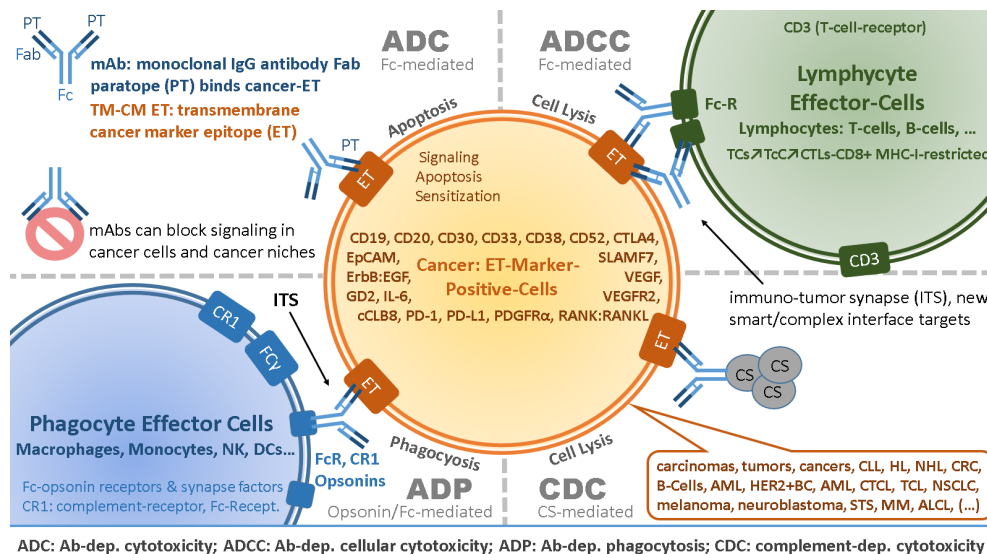


Figure 3: Biomedical Strategies and Therapeutic Mechanisms of mAbs in Immuno-Oncology

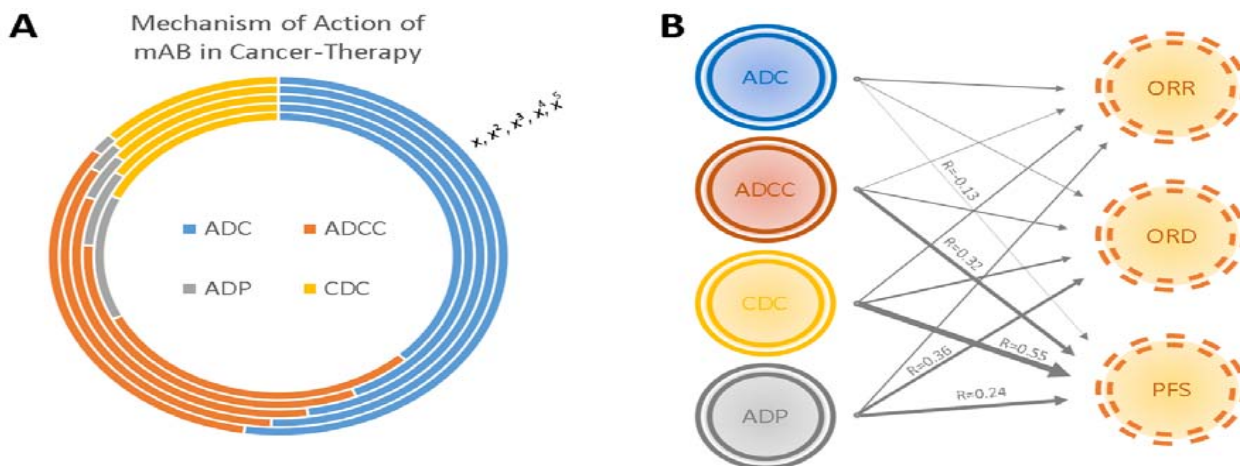
The molecular mechanisms of mAb anti-cancer drugs (Fig. 3) can be subdivided into ADC, ADCC, ADP, and CDC. ADC is the abbreviation of mAb-dependent cytotoxicity, ADCC stands for mAb-dependent cellular cytotoxicity, while ADP stands for mAb-dependent phagocytosis, and CDC abbreviates complement-dependent cytotoxicity. The overall effect of these four mechanisms of action of mAb-immunotherapy 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 labels 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.



A+B: Biomedical sketch based on scoring of simplified rough estimates to reveal the big trends and the big picture. Non-stratified Pearson correlation to reveal overall trends.

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 responsibility 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 ‘immunologic mechanism’ and its ITS interfaces might not be fully understood by today and synthetic mAbs might not fully recapitulate all ‘immunologic’ 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 immunotherapeutics 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 ITs (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-dINHL-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-cell and rituximab-ref.NHL-ORR8-14:24% PFS20	>40-50%	24	10	20	3	2	1	2	isotope, Y90 In111 beta
Bexxar®	Tositumomab +/-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 3/4SA; 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 intraocular inflammation	23	9	3,5	3	0	0	0	angiogenesis inhibitor, unconjugated
Erbix®	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, vomiting, 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% +1 n.s.	OSR4 PFS- 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%, anemia, 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
Blinicyto®	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	8,8,1 7	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
Emplicit®	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	PDGFR α	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.

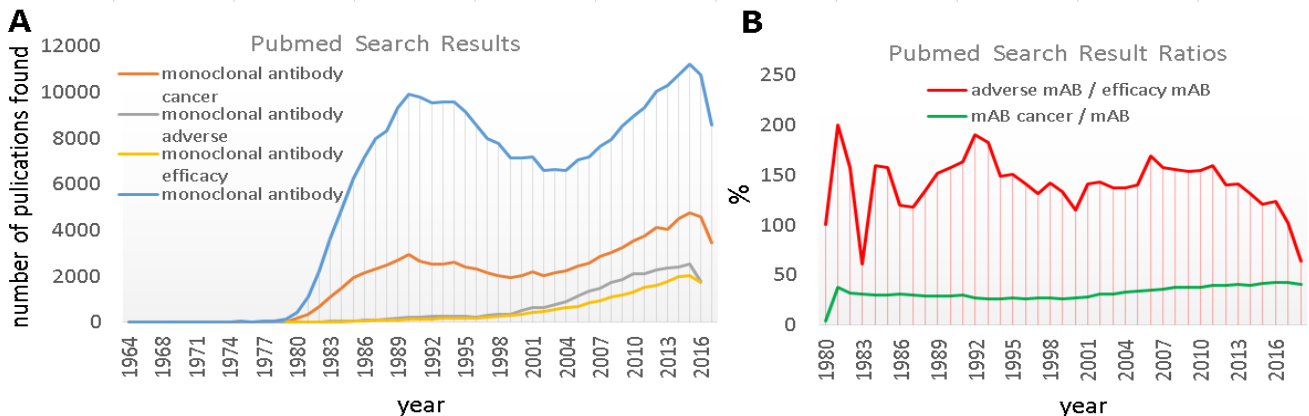


Figure 5: Pubmed search results for mAb in cancer, shown as publications per year. A: keyword “monoclonal antibody”, “cancer”, “adverse”, “efficacy”; B: ratios of adverse mAb and efficacy in %, “mAb cancer” and “mAbs” in general.

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 granzysin. 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
<i>(1) Synthetic ACT</i>	<i>Constructs</i>	<i>Cancer Types</i>	<i>Status</i>
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
<i>(2) Genetic ACT</i>	<i>Genomic Engineering & Repairing</i>	<i>Cancer Types</i>	<i>Status</i>
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 immunology 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	F D A	E M A	O R R	Res pon se	D O R	PFS	OS	Sales/p Cost/p
CAR-T, autologous, retroviral gene-therapy, 2*10^6-8/kg, following chemolympho-depletion	Yescarta-Gilead	Axicabtagene (KTE-C19)	Target: CD19, CD28/CD3-zeta chimeric antigen receptor, relapsed-type B-Cell Non-Hodgkin, Lymphoma (NHL) subtype: diffuse large B-cell lymphoma (DLBCL), DLBCL in patients who had follicular lymphoma, high grade BCL	2 0 1 7	N / A	up to 72 %	CR: 51% vs. 7% PR: 0%, 21%	9, 2	6 vs 3-4 mon th(Δ 2,5), n.r.	15,4 vs 11,2 mon th (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)	2 0 1 7	N / A	up to 83 %	up to 83% %	nr nr	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, Kimbrah 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 powerful 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.

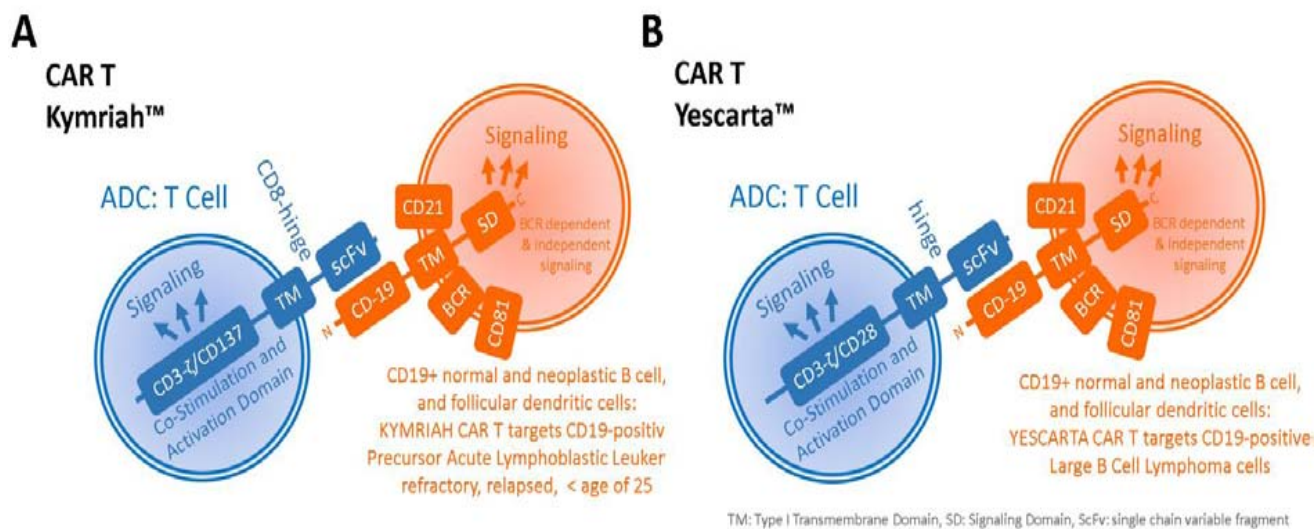


Figure 6: CAR T Mechanism and Construct Strategy of the First ACT Cancer Therapeutics, Approved 2017

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/ μ l vs 21.2 cells/ μ l; 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 efficiency 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 allogeneic 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: CD3 ζ , CD3 ζ /CD28 and CD3 ζ /4-1BB, CD3 ζ /CD28/4-1BB, or promoter/cytokine-inducible CD3 ζ /CD28/4-1BB [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 immunotherapeutics (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, PDGF α /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.

- 0. „Cytokine Priming“ Pre**
1. TCR-Antigen-HLA/MHC
2. Costimulatory Pathways

T cell:	APC:
CD28	B7-1
CTLA4	B7-2
PD-1	PD-L1
B7-1	PD-L2
Tim-3	Galectin-9
TLT-2	B7-H3
CD160	B7-H4
HVEM	HVEM
BTLA	LIGHT
CD160	ICOSL
ICOS	OX40L
OX40	CD70
CD27	4-1BBL
4-1BB	

3. Cytokine Guidance

TNF α , IL-2, IL-6, IL-12, IFN α/β , IL-21, ...?

4. Subset Polarization:

INF γ , ... ?

5. Cancer-Immuno-Feedback Signaling?

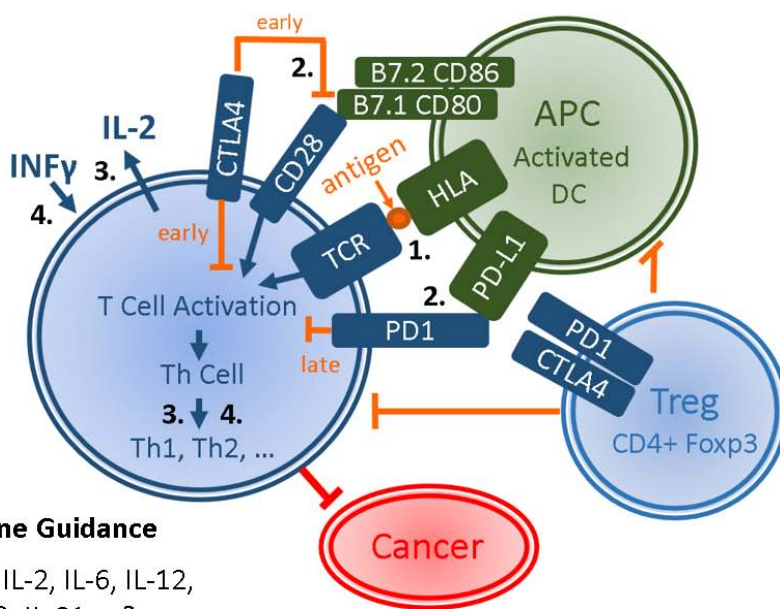


Figure 7: Costimulatory Pathways in the Activation of Helper T Cells in Cancer Immunotherapy

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 INF γ 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 difitox (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-stimulatory 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 Coley in 1891 [1], [32], [49] who injected inactivated *Streptococcus pyogenes* and *Serratia marcescens*. BCG, Bacillus Calmette-Guérin, 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-Guérin Mycobacterium bovis	bladder cancer; functions as an immunostimulatory 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	e.g., preventing recurrence of breast cancer; Her2/Neu	e.g., breast cancer, etc.	clinical trials	NeuVax from Galena Biopharma
DNA	e.g., DNA targets hTERT	e.g., intramuscular IV, many cancers	clinical trials	INO1400 from Inovio
RNA	e.g., mRNA-based-targets	e.g., melanoma and other cancers	clinical trials	gp100-mRNA
Particle	particle-adjuvants; VLPs, etc.	e.g., breast cancer, anti-relapse etc.	clinical trials	e.g., Her2/Neu
Prime-Boost	(a)heterologous (b)homologous	e.g., DNA; increased TCR avidity; CRC	clinical trials	e.g., GUCY2C-PB CRC
Tumor cells	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	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 qualitatively, 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 unbiased 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 and 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 intellectual 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 and 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 Immunotherapy 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-Guérin, 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: not 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, TGF α : 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 many 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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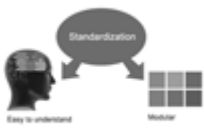
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AUXILIARY MEMBERSHIPS

Institutional Fellow of Open Association of Research Society (USA) - OARS (USA)

Global Journals Incorporation (USA) is accredited by Open Association of Research Society, U.S.A (OARS) and in turn, affiliates research institutions as “Institutional Fellow of Open Association of Research Society” (IFOARS).



The “FARSC” is a dignified title which is accorded to a person’s name viz. Dr. John E. Hall, Ph.D., FARSC or William Walldroff, M.S., FARSC.

The IFOARS institution is entitled to form a Board comprised of one Chairperson and three to five board members preferably from different streams. The Board will be recognized as “Institutional Board of Open Association of Research Society”-(IBOARS).

The Institute will be entitled to following benefits:



The IBOARS can initially review research papers of their institute and recommend them to publish with respective journal of Global Journals. It can also review the papers of other institutions after obtaining our consent. The second review will be done by peer reviewer of Global Journals Incorporation (USA) The Board is at liberty to appoint a peer reviewer with the approval of chairperson after consulting us.

The author fees of such paper may be waived off up to 40%.

The Global Journals Incorporation (USA) at its discretion can also refer double blind peer reviewed paper at their end to the board for the verification and to get recommendation for final stage of acceptance of publication.



The IBOARS can organize symposium/seminar/conference in their country on behalf of Global Journals Incorporation (USA)-OARS (USA). The terms and conditions can be discussed separately.

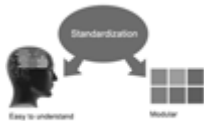
The Board can also play vital role by exploring and giving valuable suggestions regarding the Standards of “Open Association of Research Society, U.S.A (OARS)” so that proper amendment can take place for the benefit of entire research community. We shall provide details of particular standard only on receipt of request from the Board.



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We shall provide you intimation regarding launching of e-version of journal of your stream time to time. This may be utilized in your library for the enrichment of knowledge of your students as well as it can also be helpful for the concerned faculty members.



After nomination of your institution as “Institutional Fellow” and constantly functioning successfully for one year, we can consider giving recognition to your institute to function as Regional/Zonal office on our behalf. The board can also take up the additional allied activities for betterment after our consultation.

The following entitlements are applicable to individual Fellows:

Open Association of Research Society, U.S.A (OARS) By-laws states that an individual Fellow may use the designations as applicable, or the corresponding initials. The Credentials of individual Fellow and Associate designations signify that the individual has gained knowledge of the fundamental concepts. One is magnanimous and proficient in an expertise course covering the professional code of conduct, and follows recognized standards of practice.



Open Association of Research Society (US)/ Global Journals Incorporation (USA), as described in Corporate Statements, are educational, research publishing and professional membership organizations. Achieving our individual Fellow or Associate status is based mainly on meeting stated educational research requirements.

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We shall provide print version of 12 issues of any three journals [as per your requirement] out of our 38 journals worth \$ 2376 USD.

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- The professional accredited with Fellow honor, is entitled to various benefits viz. name, fame, honor, regular flow of income, secured bright future, social status etc.



- In addition to above, if one is single author, then entitled to 40% discount on publishing research paper and can get 10% discount if one is co-author or main author among group of authors.
- The Fellow can organize symposium/seminar/conference on behalf of Global Journals Incorporation (USA) and he/she can also attend the same organized by other institutes on behalf of Global Journals.
- The Fellow can become member of Editorial Board Member after completing 3yrs.
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- • This individual has learned the basic methods of applying those concepts and techniques to common challenging situations. This individual has further demonstrated an in-depth understanding of the application of suitable techniques to a particular area of research practice.

Note :

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- In future, if the board feels the necessity to change any board member, the same can be done with the consent of the chairperson along with anyone board member without our approval.
- In case, the chairperson needs to be replaced then consent of 2/3rd board members are required and they are also required to jointly pass the resolution copy of which should be sent to us. In such case, it will be compulsory to obtain our approval before replacement.
- In case of “Difference of Opinion [if any]” among the Board members, our decision will be final and binding to everyone.

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PREFERRED AUTHOR GUIDELINES

We accept the manuscript submissions in any standard (generic) format.

We typeset manuscripts using advanced typesetting tools like Adobe In Design, CorelDraw, TeXnicCenter, and TeXStudio. We usually recommend authors submit their research using any standard format they are comfortable with, and let Global Journals do the rest.

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2. Authors must accept the privacy policy, terms, and conditions of Global Journals.
3. Ensure corresponding author's email address and postal address are accurate and reachable.
4. Manuscript to be submitted must include keywords, an abstract, a paper title, co-author(s') names and details (email address, name, phone number, and institution), figures and illustrations in vector format including appropriate captions, tables, including titles and footnotes, a conclusion, results, acknowledgments and references.
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- Findings
- Writings
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- Any other original work

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Acknowledgments

Contributors to the research other than authors credited should be mentioned in Acknowledgments. The source of funding for the research can be included. Suppliers of resources may be mentioned along with their addresses.

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PREPARING YOUR MANUSCRIPT

Authors can submit papers and articles in an acceptable file format: MS Word (doc, docx), LaTeX (.tex, .zip or .rar including all of your files), Adobe PDF (.pdf), rich text format (.rtf), simple text document (.txt), Open Document Text (.odt), and Apple Pages (.pages). Our professional layout editors will format the entire paper according to our official guidelines. This is one of the highlights of publishing with Global Journals—authors should not be concerned about the formatting of their paper. Global Journals accepts articles and manuscripts in every major language, be it Spanish, Chinese, Japanese, Portuguese, Russian, French, German, Dutch, Italian, Greek, or any other national language, but the title, subtitle, and abstract should be in English. This will facilitate indexing and the pre-peer review process.

The following is the official style and template developed for publication of a research paper. Authors are not required to follow this style during the submission of the paper. It is just for reference purposes.



Manuscript Style Instruction (Optional)

- Microsoft Word Document Setting Instructions.
- Font type of all text should be Swis721 Lt BT.
- Page size: 8.27" x 11", left margin: 0.65, right margin: 0.65, bottom margin: 0.75.
- Paper title should be in one column of font size 24.
- Author name in font size of 11 in one column.
- Abstract: font size 9 with the word "Abstract" in bold italics.
- Main text: font size 10 with two justified columns.
- Two columns with equal column width of 3.38 and spacing of 0.2.
- First character must be three lines drop-capped.
- The paragraph before spacing of 1 pt and after of 0 pt.
- Line spacing of 1 pt.
- Large images must be in one column.
- The names of first main headings (Heading 1) must be in Roman font, capital letters, and font size of 10.
- The names of second main headings (Heading 2) must not include numbers and must be in italics with a font size of 10.

Structure and Format of Manuscript

The recommended size of an original research paper is under 15,000 words and review papers under 7,000 words. Research articles should be less than 10,000 words. Research papers are usually longer than review papers. Review papers are reports of significant research (typically less than 7,000 words, including tables, figures, and references)

A research paper must include:

- a) A title which should be relevant to the theme of the paper.
- b) A summary, known as an abstract (less than 150 words), containing the major results and conclusions.
- c) Up to 10 keywords that precisely identify the paper's subject, purpose, and focus.
- d) An introduction, giving fundamental background objectives.
- e) Resources and techniques with sufficient complete experimental details (wherever possible by reference) to permit repetition, sources of information must be given, and numerical methods must be specified by reference.
- f) Results which should be presented concisely by well-designed tables and figures.
- g) Suitable statistical data should also be given.
- h) All data must have been gathered with attention to numerical detail in the planning stage.

Design has been recognized to be essential to experiments for a considerable time, and the editor has decided that any paper that appears not to have adequate numerical treatments of the data will be returned unrefereed.

- i) Discussion should cover implications and consequences and not just recapitulate the results; conclusions should also be summarized.
- j) There should be brief acknowledgments.
- k) There ought to be references in the conventional format. Global Journals recommends APA format.

Authors should carefully consider the preparation of papers to ensure that they communicate effectively. Papers are much more likely to be accepted if they are carefully designed and laid out, contain few or no errors, are summarizing, and follow instructions. They will also be published with much fewer delays than those that require much technical and editorial correction.

The Editorial Board reserves the right to make literary corrections and suggestions to improve brevity.

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All manuscripts submitted to Global Journals should include:

Title

The title page must carry an informative title that reflects the content, a running title (less than 45 characters together with spaces), names of the authors and co-authors, and the place(s) where the work was carried out.

Author details

The full postal address of any related author(s) must be specified.

Abstract

The abstract is the foundation of the research paper. It should be clear and concise and must contain the objective of the paper and inferences drawn. It is advised to not include big mathematical equations or complicated jargon.

Many researchers searching for information online will use search engines such as Google, Yahoo or others. By optimizing your paper for search engines, you will amplify the chance of someone finding it. In turn, this will make it more likely to be viewed and cited in further works. Global Journals has compiled these guidelines to facilitate you to maximize the web-friendliness of the most public part of your paper.

Keywords

A major lynchpin of research work for the writing of research papers is the keyword search, which one will employ to find both library and internet resources. Up to eleven keywords or very brief phrases have to be given to help data retrieval, mining, and indexing.

One must be persistent and creative in using keywords. An effective keyword search requires a strategy: planning of a list of possible keywords and phrases to try.

Choice of the main keywords is the first tool of writing a research paper. Research paper writing is an art. Keyword search should be as strategic as possible.

One should start brainstorming lists of potential keywords before even beginning searching. Think about the most important concepts related to research work. Ask, "What words would a source have to include to be truly valuable in a research paper?" Then consider synonyms for the important words.

It may take the discovery of only one important paper to steer in the right keyword direction because, in most databases, the keywords under which a research paper is abstracted are listed with the paper.

Numerical Methods

Numerical methods used should be transparent and, where appropriate, supported by references.

Abbreviations

Authors must list all the abbreviations used in the paper at the end of the paper or in a separate table before using them.

Formulas and equations

Authors are advised to submit any mathematical equation using either MathJax, KaTeX, or LaTeX, or in a very high-quality image.

Tables, Figures, and Figure Legends

Tables: Tables should be cautiously designed, uncrowned, and include only essential data. Each must have an Arabic number, e.g., Table 4, a self-explanatory caption, and be on a separate sheet. Authors must submit tables in an editable format and not as images. References to these tables (if any) must be mentioned accurately.



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Figures are supposed to be submitted as separate files. Always include a citation in the text for each figure using Arabic numbers, e.g., Fig. 4. Artwork must be submitted online in vector electronic form or by emailing it.

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Although low-quality images are sufficient for review purposes, print publication requires high-quality images to prevent the final product being blurred or fuzzy. Submit (possibly by e-mail) EPS (line art) or TIFF (halftone/ photographs) files only. MS PowerPoint and Word Graphics are unsuitable for printed pictures. Avoid using pixel-oriented software. Scans (TIFF only) should have a resolution of at least 350 dpi (halftone) or 700 to 1100 dpi (line drawings). Please give the data for figures in black and white or submit a Color Work Agreement form. EPS files must be saved with fonts embedded (and with a TIFF preview, if possible).

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TIPS FOR WRITING A GOOD QUALITY MEDICAL RESEARCH PAPER

1. Choosing the topic: In most cases, the topic is selected by the interests of the author, but it can also be suggested by the guides. You can have several topics, and then judge which you are most comfortable with. This may be done by asking several questions of yourself, like "Will I be able to carry out a search in this area? Will I find all necessary resources to accomplish the search? Will I be able to find all information in this field area?" If the answer to this type of question is "yes," then you ought to choose that topic. In most cases, you may have to conduct surveys and visit several places. Also, you might have to do a lot of work to find all the rises and falls of the various data on that subject. Sometimes, detailed information plays a vital role, instead of short information. Evaluators are human: The first thing to remember is that evaluators are also human beings. They are not only meant for rejecting a paper. They are here to evaluate your paper. So present your best aspect.

2. Think like evaluators: If you are in confusion or getting demotivated because your paper may not be accepted by the evaluators, then think, and try to evaluate your paper like an evaluator. Try to understand what an evaluator wants in your research paper, and you will automatically have your answer. Make blueprints of paper: The outline is the plan or framework that will help you to arrange your thoughts. It will make your paper logical. But remember that all points of your outline must be related to the topic you have chosen.

3. Ask your guides: If you are having any difficulty with your research, then do not hesitate to share your difficulty with your guide (if you have one). They will surely help you out and resolve your doubts. If you can't clarify what exactly you require for your work, then ask your supervisor to help you with an alternative. He or she might also provide you with a list of essential readings.

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7. Revise what you wrote: When you write anything, always read it, summarize it, and then finalize it.

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12. Know what you know: Always try to know what you know by making objectives, otherwise you will be confused and unable to achieve your target.

13. Use good grammar: Always use good grammar and words that will have a positive impact on the evaluator; use of good vocabulary does not mean using tough words which the evaluator has to find in a dictionary. Do not fragment sentences. Eliminate one-word sentences. Do not ever use a big word when a smaller one would suffice.

Verbs have to be in agreement with their subjects. In a research paper, do not start sentences with conjunctions or finish them with prepositions. When writing formally, it is advisable to never split an infinitive because someone will (wrongly) complain. Avoid clichés like a disease. Always shun irritating alliteration. Use language which is simple and straightforward. Put together a neat summary.

14. Arrangement of information: Each section of the main body should start with an opening sentence, and there should be a changeover at the end of the section. Give only valid and powerful arguments for your topic. You may also maintain your arguments with records.

15. Never start at the last minute: Always allow enough time for research work. Leaving everything to the last minute will degrade your paper and spoil your work.

16. Multitasking in research is not good: Doing several things at the same time is a bad habit in the case of research activity. Research is an area where everything has a particular time slot. Divide your research work into parts, and do a particular part in a particular time slot.

17. Never copy others' work: Never copy others' work and give it your name because if the evaluator has seen it anywhere, you will be in trouble. Take proper rest and food: No matter how many hours you spend on your research activity, if you are not taking care of your health, then all your efforts will have been in vain. For quality research, take proper rest and food.

18. Go to seminars: Attend seminars if the topic is relevant to your research area. Utilize all your resources.

19. Refresh your mind after intervals: Try to give your mind a rest by listening to soft music or sleeping in intervals. This will also improve your memory. Acquire colleagues: Always try to acquire colleagues. No matter how sharp you are, if you acquire colleagues, they can give you ideas which will be helpful to your research.



20. Think technically: Always think technically. If anything happens, search for its reasons, benefits, and demerits. Think and then print: When you go to print your paper, check that tables are not split, headings are not detached from their descriptions, and page sequence is maintained.

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23. Upon conclusion: Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium through which your research is going to be in print for the rest of the crowd. Care should be taken to categorize your thoughts well and present them in a logical and neat manner. A good quality research paper format is essential because it serves to highlight your research paper and bring to light all necessary aspects of your research.

INFORMAL GUIDELINES OF RESEARCH PAPER WRITING

Key points to remember:

- Submit all work in its final form.
- Write your paper in the form which is presented in the guidelines using the template.
- Please note the criteria peer reviewers will use for grading the final paper.

Final points:

One purpose of organizing a research paper is to let people interpret your efforts selectively. The journal requires the following sections, submitted in the order listed, with each section starting on a new page:

The introduction: This will be compiled from reference matter and reflect the design processes or outline of basis that directed you to make a study. As you carry out the process of study, the method and process section will be constructed like that. The results segment will show related statistics in nearly sequential order and direct reviewers to similar intellectual paths throughout the data that you gathered to carry out your study.

The discussion section:

This will provide understanding of the data and projections as to the implications of the results. The use of good quality references throughout the paper will give the effort trustworthiness by representing an alertness to prior workings.

Writing a research paper is not an easy job, no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record-keeping are the only means to make straightforward progression.

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Specific editorial column necessities for compliance of a manuscript will always take over from directions in these general guidelines.

To make a paper clear: Adhere to recommended page limits.



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- Insertion of a title at the foot of a page with subsequent text on the next page.
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- Submitting a manuscript with pages out of sequence.
- In every section of your document, use standard writing style, including articles ("a" and "the").
- Keep paying attention to the topic of the paper.
- Use paragraphs to split each significant point (excluding the abstract).
- Align the primary line of each section.
- Present your points in sound order.
- Use present tense to report well-accepted matters.
- Use past tense to describe specific results.
- Do not use familiar wording; don't address the reviewer directly. Don't use slang or superlatives.
- Avoid use of extra pictures—include only those figures essential to presenting results.

Title page:

Choose a revealing title. It should be short and include the name(s) and address(es) of all authors. It should not have acronyms or abbreviations or exceed two printed lines.

Abstract: This summary should be two hundred words or less. It should clearly and briefly explain the key findings reported in the manuscript and must have precise statistics. It should not have acronyms or abbreviations. It should be logical in itself. Do not cite references at this point.

An abstract is a brief, distinct paragraph summary of finished work or work in development. In a minute or less, a reviewer can be taught the foundation behind the study, common approaches to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Use comprehensive sentences, and do not sacrifice readability for brevity; you can maintain it succinctly by phrasing sentences so that they provide more than a lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study with the subsequent elements in any summary. Try to limit the initial two items to no more than one line each.

Reason for writing the article—theory, overall issue, purpose.

- Fundamental goal.
- To-the-point depiction of the research.
- Consequences, including definite statistics—if the consequences are quantitative in nature, account for this; results of any numerical analysis should be reported. Significant conclusions or questions that emerge from the research.

Approach:

- Single section and succinct.
- An outline of the job done is always written in past tense.
- Concentrate on shortening results—limit background information to a verdict or two.
- Exact spelling, clarity of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else.

Introduction:

The introduction should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable of comprehending and calculating the purpose of your study without having to refer to other works. The basis for the study should be offered. Give the most important references, but avoid making a comprehensive appraisal of the topic. Describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will give no attention to your results. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here.



The following approach can create a valuable beginning:

- Explain the value (significance) of the study.
- Defend the model—why did you employ this particular system or method? What is its compensation? Remark upon its appropriateness from an abstract point of view as well as pointing out sensible reasons for using it.
- Present a justification. State your particular theory(-ies) or aim(s), and describe the logic that led you to choose them.
- Briefly explain the study's tentative purpose and how it meets the declared objectives.

Approach:

Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done. Sort out your thoughts; manufacture one key point for every section. If you make the four points listed above, you will need at least four paragraphs. Present surrounding information only when it is necessary to support a situation. The reviewer does not desire to read everything you know about a topic. Shape the theory specifically—do not take a broad view.

As always, give awareness to spelling, simplicity, and correctness of sentences and phrases.

Procedures (methods and materials):

This part is supposed to be the easiest to carve if you have good skills. A soundly written procedures segment allows a capable scientist to replicate your results. Present precise information about your supplies. The suppliers and clarity of reagents can be helpful bits of information. Present methods in sequential order, but linked methodologies can be grouped as a segment. Be concise when relating the protocols. Attempt to give the least amount of information that would permit another capable scientist to replicate your outcome, but be cautious that vital information is integrated. The use of subheadings is suggested and ought to be synchronized with the results section.

When a technique is used that has been well-described in another section, mention the specific item describing the way, but draw the basic principle while stating the situation. The purpose is to show all particular resources and broad procedures so that another person may use some or all of the methods in one more study or referee the scientific value of your work. It is not to be a step-by-step report of the whole thing you did, nor is a methods section a set of orders.

Materials:

Materials may be reported in part of a section or else they may be recognized along with your measures.

Methods:

- Report the method and not the particulars of each process that engaged the same methodology.
- Describe the method entirely.
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures.
- Simplify—detail how procedures were completed, not how they were performed on a particular day.
- If well-known procedures were used, account for the procedure by name, possibly with a reference, and that's all.

Approach:

It is embarrassing to use vigorous voice when documenting methods without using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result, when writing up the methods, most authors use third person passive voice.

Use standard style in this and every other part of the paper—avoid familiar lists, and use full sentences.

What to keep away from:

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings—save it for the argument.
- Leave out information that is immaterial to a third party.



Results:

The principle of a results segment is to present and demonstrate your conclusion. Create this part as entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Use statistics and tables, if suitable, to present consequences most efficiently.

You must clearly differentiate material which would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matters should not be submitted at all except if requested by the instructor.

Content:

- Sum up your conclusions in text and demonstrate them, if suitable, with figures and tables.
- In the manuscript, explain each of your consequences, and point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation of an exacting study.
- Explain results of control experiments and give remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or manuscript.

What to stay away from:

- Do not discuss or infer your outcome, report surrounding information, or try to explain anything.
- Do not include raw data or intermediate calculations in a research manuscript.
- Do not present similar data more than once.
- A manuscript should complement any figures or tables, not duplicate information.
- Never confuse figures with tables—there is a difference.

Approach:

As always, use past tense when you submit your results, and put the whole thing in a reasonable order.

Put figures and tables, appropriately numbered, in order at the end of the report.

If you desire, you may place your figures and tables properly within the text of your results section.

Figures and tables:

If you put figures and tables at the end of some details, make certain that they are visibly distinguished from any attached appendix materials, such as raw facts. Whatever the position, each table must be titled, numbered one after the other, and include a heading. All figures and tables must be divided from the text.

Discussion:

The discussion is expected to be the trickiest segment to write. A lot of papers submitted to the journal are discarded based on problems with the discussion. There is no rule for how long an argument should be.

Position your understanding of the outcome visibly to lead the reviewer through your conclusions, and then finish the paper with a summing up of the implications of the study. The purpose here is to offer an understanding of your results and support all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of results should be fully described.

Infer your data in the conversation in suitable depth. This means that when you clarify an observable fact, you must explain mechanisms that may account for the observation. If your results vary from your prospect, make clear why that may have happened. If your results agree, then explain the theory that the proof supported. It is never suitable to just state that the data approved the prospect, and let it drop at that. Make a decision as to whether each premise is supported or discarded or if you cannot make a conclusion with assurance. Do not just dismiss a study or part of a study as "uncertain."



Research papers are not acknowledged if the work is imperfect. Draw what conclusions you can based upon the results that you have, and take care of the study as a finished work.

- You may propose future guidelines, such as how an experiment might be personalized to accomplish a new idea.
- Give details of all of your remarks as much as possible, focusing on mechanisms.
- Make a decision as to whether the tentative design sufficiently addressed the theory and whether or not it was correctly restricted. Try to present substitute explanations if they are sensible alternatives.
- One piece of research will not counter an overall question, so maintain the large picture in mind. Where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

Approach:

When you refer to information, differentiate data generated by your own studies from other available information. Present work done by specific persons (including you) in past tense.

Describe generally acknowledged facts and main beliefs in present tense.

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	A-B	C-D	E-F
<i>Abstract</i>	Clear and concise with appropriate content, Correct format. 200 words or below	Unclear summary and no specific data, Incorrect form Above 200 words	No specific data with ambiguous information Above 250 words
<i>Introduction</i>	Containing all background details with clear goal and appropriate details, flow specification, no grammar and spelling mistake, well organized sentence and paragraph, reference cited	Unclear and confusing data, appropriate format, grammar and spelling errors with unorganized matter	Out of place depth and content, hazy format
<i>Methods and Procedures</i>	Clear and to the point with well arranged paragraph, precision and accuracy of facts and figures, well organized subheads	Difficult to comprehend with embarrassed text, too much explanation but completed	Incorrect and unorganized structure with hazy meaning
<i>Result</i>	Well organized, Clear and specific, Correct units with precision, correct data, well structuring of paragraph, no grammar and spelling mistake	Complete and embarrassed text, difficult to comprehend	Irregular format with wrong facts and figures
<i>Discussion</i>	Well organized, meaningful specification, sound conclusion, logical and concise explanation, highly structured paragraph reference cited	Wordy, unclear conclusion, spurious	Conclusion is not cited, unorganized, difficult to comprehend
<i>References</i>	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring



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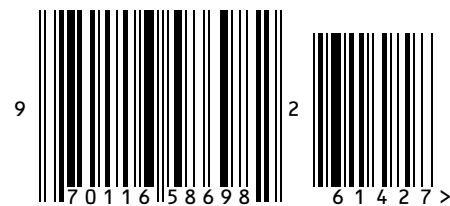
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