Electrodynamic Binning Theory versus Induced Fit Theory

Significant implification for the engineering of therapeutic antibodies

Udo Riss

DRE-Dr. Riss Ellipsometerbau GmbH, Feldstr. 14, 23909 Ratzeburg, Germany
dr.riss@dre.de

***Abstract*—We compared the induced fit theory with the electrodynamic binning theory for the interaction between antibodies and antigens. For the induced fit theory we found 8 knock-out criteria which reduce the probability for the correctness of this theory to 0.000003%; for the electrodynamic binning theory we calculated a probability of 99.9999999%. Main reason for this is that the electrodynamic binning theory can calculate the contribution of the antibody constant regions to affinity and specificity.**

Keywords- Antibody; Antigen; Induced fit; Electrodynamic binning;Therapeutic antibodies

I. INTRODUCTION

In 2011 we developed a theory to explain the binning curves of highly specific IgE-antibodies to recombinant antigens [1]. The measured binning curve of an antibody was different from the binning curve expected from the law of mass action if the antibody was not labelled but it was in accordance with the law of mass action if the antibody was labelled with a 40 nm gold particle. And so we concluded that binning cannot be caused by direct chemical interaction. Instead of direct chemical binding/binning our electrodynamic binning theory is based on electrodynamic interaction between antibodies and antigens. Antibodies have a motor, a steering unit and a detection system for antigenic determinants.

We started with a mathematical analysis of the principle and showed that electrodynamic interaction can explain both the binning curves of unlabeled antibodies and labelled antibodies from mathematical point of view [1].

In addition to these measurements and mathematical analysis [1] we used third party measurements to calculate the probabilities for our electrodynamic binning theory compared to the currently used induced fit theory which is based on chemical interaction.

II. INDUCED FIT THEORY

In 1984 Emil Fischer developed the lock and key principle for the interaction between substrates and enzymes. After finding that this concept cannot describe the substrate-enzyme interaction correctly D. E. Koshland [2] developed the concept of induced fit in 1958. Induced fit means that the molecules change their atomic configuration so that a fit can be done between enzyme and substrate. A mathematical or physical description of this process was not done. The induced fit model was accepted because it was the only concept in accordance with the dogma that the binding/binning between substrate and enzyme is of chemical nature.

This model was transferred to the interaction between antibody and antigen. The induced fit theory is the currently accepted theoretical model for antibody-antigen interactions. Development of therapeutic antibodies is currently based on the concept of induced fit.

III. ARGUMENTS AGAINST INDUCED FIT THEORY AND DIRECT CHEMICAL BINDING/BINNING

Eight very strong arguments (knock-out criteria) can be found which are in contrast to the induced fit theory based on direct binding/binning.

1. The induced fit process requires energy because the molecular structure of antibodies must be rearranged for induced fitting. No energy source for the induced fit process is known.
2. X-ray measurements have shown that only 30% of the complementarity determining regions (CDRs) of an antibody are in contact with the antigen and the contact area between antibody CDRs and antigen is relatively flat [3]. And so the authors assumed that other effects like electrostatics and hydrogen bonds must have a significant influence.
3. Further arguments against direct binding/binning are the symmetric bispecific antibodies developed by X-Body Biosciences [4]. They have produced antibodies where the light chain has affinity to a different antigen than the heavy chain. This antibody type is not possible if chemical binding/binning (induced fit) is responsible for the binding/binning effect.
4. Also the finding of Alexandre Rothen [5] that buried antigens are attracting antibodies is in contrast with the induced fit theory. And so he stated: *"Great difficulty is therefore encountered in trying to explain such phenomena on the basis of the current chemical theories which axiomatically assume that the reaction occurs between groups of the antigen and definite groups of the antibody. If this were the case, how could definite groups of antibody molecule react with definite groups of the antigen film buried under seven layer of the same antigen 56 Å deep?"*
5. We put a 7 nm Si_3N_4-membrane between antigen and

antibody and found that antibodies are still attracted by antigens. The experimental setup is described in [6].

6. Argument No. 6 against direct chemical binding/binning is that FAB-fragments can have lower affinity than a full-size antibody with same Fabs [7].
7. Seventh argument against induced fit is the experimental fact that the constant region of an antibody have an influence on affinity and specificity of an antibody. 11 independent groups have found this effect in different setups [8,9,10,11,12,13,14,15,16,17,18,19,20, and 21]. All these papers are in contrast to the dogma of direct chemical binding/binning, because they have found a significant influence of the constant region which is not in contact with the antigen.
8. The last argument against direct binding/binning is that direct binding/binning cannot explain the long distance interaction we have discovered [1].

All together we have 8 independent knock-out criteria for the induced fit theory measured by 17 independent groups.

Assuming the worst case that only 50% of the independent groups are working scientifically correct (which means that the other 50% are working as good as they can but they are making errors from scientific point of view), and assuming that 50% of the measurements can be equipped with artefacts and assuming that both events are independent we calculate a probability of 99.999997% that the induced fit theory is wrong. That means that there is only a chance of 0.000003% that the induced fit theory and direct chemical binding/binning is a true theory supported by experimental measurements.

IV. ELECTRODYNAMIC BINNING THEORY

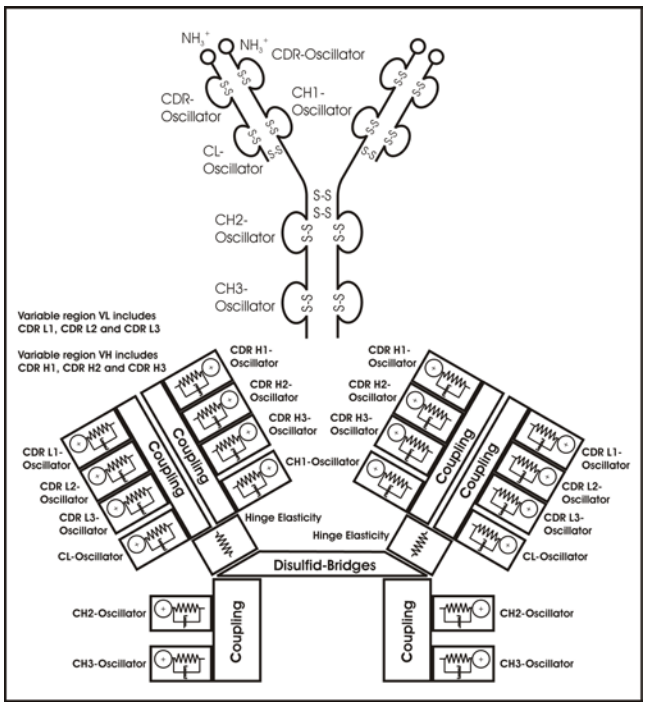

Fig. 1: Block diagram of an IgG-antibody according to the Electrodynamic Binning Theory

Fig. 1 shows the block diagram of an antibody according to our electrodynamic binning theory. The antibody is split into the functional groups VL, VH, CL, CH1, CH2, CH3, and hinge region. The group VL is build by the three CDR-oscillators CDR-L1, CDR-L2, and CDR-L3; the group VH is build by the CDR-oscillators CDR-H1, CDR-H2, and CDR-H3. As constant heavy chain group oscillators we have the CH1, the CH2 and the CH3-oscillator, and as light chain group oscillator we have only the CL-oscillator. All oscillators are able to oscillate in the terahertz range and are coupled by coupling systems. Additional to these couplings we have the elasticity of the hinge region, which is very important for phase locking to an external electromagnetic field.

When searching for a target the oscillation energy is permanently transferred from one arm of the antibody to the other. This results in a permanent change of phase of the electromagnetic wave. An external electrodynamic field of same frequency leads to phase locking; the antibody has detected the antigenic components. The hinge elasticity is very important for phase locking. Mathematical analysis showed that phase locking would not be possible without hinge elasticity [1].

The knowledge that the induced fit theory and the theory of direct molecular binding/binning is wrong does not implement automatically that our electrodynamic binning theory is true. At first all required components for our theory must be found.

The first requirement of our theory is that we must have springs, masses and electrical charges in the molecule. Each molecule has a mass, NH_3^+ ions are found as charges, beta-sheets and alpha-helices are found as springs [22, 23, 24, 25, and 26]. So we have all components we need for building up an electromagnetic oscillator.

The second requirement is that an antibody is able to oscillate in the terahertz frequency range (THz) and that an antigen is also able to oscillate in the terahertz range. It is known that there is an antibody-antigen interaction in the THz-range [27] and Peter Ortoleva has discovered that a virus is emitting THz-waves [28, 29].

The third requirement is that the antibody must have twisted arms (heavy and light chain) otherwise the antibody would not be able to rotate. This required twisting of the antibody chains was found [30], but in contrast to the shown rotation the antibody would rotate in the opposite direction.

Additional to these requirements the electrodynamic binning theory has no problems with the knock-out criteria of the induced fit theory.

1. Energy supply is known; energy is coming from Brownian Movement. Parts that hit the oscillators create Dirac-pulses (Dirac-delta function) that bring energy to the corresponding oscillators.
2. The CDRs must not be in direct contact with the antigen, because the electric fields are coupling in phase. So it is no problem if only 30% of the CDRs are connected with the antigen.

3. Each CDR can show affinity to a different antigen. So the antibody produced by X-Body Biosciences is possible with the electrodynamic binning theory.
4. The theory is also supported by the measurements of Alexandre Rothen. Buried antigens can attract antibodies.
5. A 7 nm membrane between antibody and antigen does not suppress antibody-antigen interaction. This is also explainable with the electrodynamic binning theory.
6. Fab-fragments can have lower affinity compared to full-size antibodies because the constant regions (mainly the hinge region) have an influence on oscillation frequency.
7. The measurements [8,9,10,11,12,13,14,15,16,17,18,19, 20, and 21] which demonstrate that the constant regions has a big influence on affinity and specificity of antibodies can be calculated and explained exactly.
8. The long distance force was the reason for developing the electrodynamic binning theory. So it is in accordance with the electrodynamic binning theory.

Marcella Torres and Arturo Casedeval have defined 5 questions in their review "*The immunoglobulin constant region contributes to affinity and specificity"* [11] which can be answered with the electrodynamic binning theory:

1. Are class switch recombinations and VDJ recombinations linked to produce Abs of particular isotype?
   A**nswer: No**
2. How does isotype alter the idiotype response?
   Answer: This is calculable.
3. Does the V-region type affect CH-region function?
   A**nswer: The V-region does not but can affect CH-region function. In worst case the antibodies become autoantibodies.**
4. What are the crucial residues that are permissive for the transmission of structural effects from the CH region to the V-region and vice versa?
   Answer: This is calculable with the electrodynamic binning theory.
5. If CH-region type affects specificity, how does one separate the effects of changed specificity from different CH-conferred effector functions when assessing the relative efficacy of different AB isotypes against microbes and tumors?
   Answer: This is calculable. The antibody is not able to bind, if a tumor is detected as friend; microbes are always identified as foe.

Additional there are further effects which can be explained with the electrodynamic binning theory.

Labelled antibodies are losing their capability of long distance detection because the external load suppresses the synchronous rotation of the antibody. That means antibodies with linked toxophores have lost their long distance detection system. This effect is calculable with mathematics. And it is an effect that is very important for designing therapeutic antibodies.

Viruses, bacteria and dendritic cells are not only emitting THz-waves they are also emitting low frequency radio signals. This effect was found for viruses and bacteria by Luc Montagnier [31, 32]. He thought that theses signals are coming from DNA, but according to our theory these signals are coming from the membranes of the viruses and bacteria. Our theory states that viruses, bacteria and dendritic cells have a motor, a steering unit and a detection system as antibodies have. For a virus we have found this effect. A dendritic cell is moving in direction to high chemokine concentration which can be interpreted as such a controlled mechanism. For a bacterium prove of principle is pending. Fig. 2 shows the principle of a virus, a bacterium or a dendritic cell.

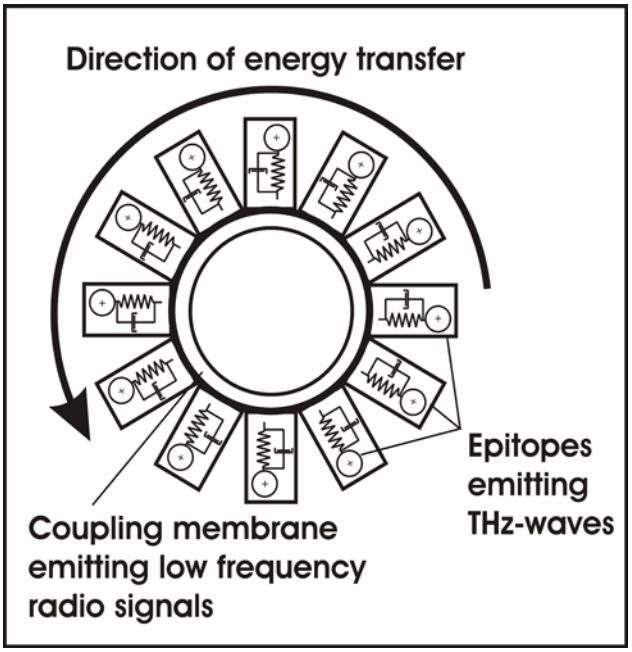

Fig. 2: Principle of a virus, a bacterium or a dendritic cell

Each epitope is a terahertz-wave oscillator that is coupled to neighboured oscillators via a membrane. The energy transfer is producing a low frequency radio signal (frequency of phase modulation). The low frequency radio signal stops if the phase is locked to the THz-wave of an external target.

ScFv and BiTe-antibodies need a linker of definite size. Without this linker, affinity and specificity of these single chain antibodies reduces. This effect is also expected from the electrodynamic binning theory. For getting high affinity and specificity the linker must simulate elasticity of the hinge region (and the connected constant region) of the full-size antibody from which the scFv or BiTe-antibody components are taken. The block diagrams of a scFv antibody and a full-size antibody are shown in Fig. 3.

All together we have found 17 independent effects measured by 23 independent groups that support our electrodynamic binning theory. Assuming that in worst case only 50% of the independent groups are working scientifically correct (which means that the other groups are making errors from scientific point of view), and assuming that 50% of the measurements can be equipped with

artefacts and assuming that both events are independent, because every body is working as good as he can, we can calculate a probability of 99.9999999% that the electrodynamic binning theory is correct.

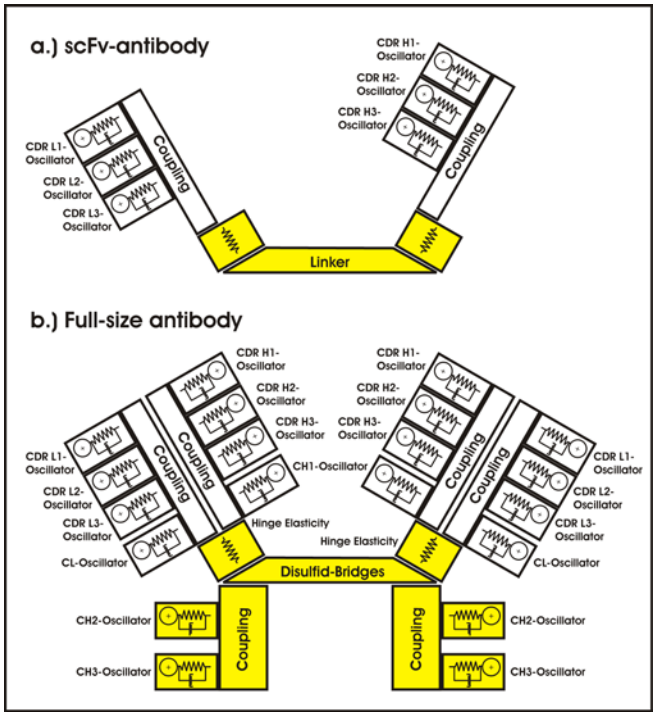

Fig. 3: Block diagram of a scFv-single chain antibody compared to a full-size antibody. For correct working the linker (yellow) of the scFv-antibody must simulate the hinge and connected constant region of a full-size antibody (yellow).

V. MESSENGER MOLECULES

We think the electrodynamic principle is not only limited to antibodies, viruses, bacteria and dendritic cells. We have beta-sheets and alpha-helices in enzymes and substrates and a lot of other molecules. Messenger molecules are also equipped with molecular electrical charges and springs (alpha-helices, beta-sheets), and so we think signal transfer of messenger molecules is based on electrodynamic effects and not on chemical binding/binning. To support this theory we used simple mathematics.

Electrostatics and molecular forces have a detection range of maximal 3 nm, so the sphere for chemical interaction has a volume of 113.1 nm^3. When transporting a signal over a distance of 1 micron to a target we have a sphere of about 4188790205 nm^3. That means the probability that the molecule takes the shortest way to the target is $2.7*10^{-8}$. In this case it is very improbable that the messenger molecule reaches the target. Even if the distance to the target is only 10 nm we have a probability of only 2.7% that the messenger molecule takes the shortest way to the target. Compared to this low probability our electrodynamic binning theory has a 100% reliable signal transfer.

But this does not mean that no messenger molecule is moving to its target. For some messenger molecules we have found structures that can be interpreted as motor, steering unit and detecting system. In this case the messenger molecule can locate the target via phase locking of electromagnetic waves and than it is moving directly to the target. We think for example that Interleukin 6 has a motor, a steering unit and a detection system. In contrast to this we think that the Tau-protein is not able to move in a controlled way, we are expecting only rotation of the molecule.

VI. MATHEMATICS OF ELECTRODYNAMIC BINNING THEORY

The electrodynamic binning theory is based on mathematics. A full-size antibody can be split into the functional groups VL, VH, CL, CH1, CH2, CH3, hinge region etc. (Fig. 1). Each of these functional groups can be described by a tensor differential equation of higher rank. Each functional group can be coupled to other functional groups by coupling systems. So it is possible to simulate an antibody completely. An antigen can be described very easy by a single tensor differential equation if the antigen has only one beta-sheet without damping. Then it is very easy to calculate the interaction of the antigen tensor differential equation with the tensor differential equations of the functional groups of an antibody (VL, VH, CL, CH1, CH2, CH3, hinge region etc.).

But if one of these groups has damping mathematics will be on a significant higher level. In this case the hits of parts from Brownian Movement must be taken into account, because each hit can be interpreted as Dirac-pulse that leads to a phase jump of oscillation. A big number of hits lead to an increase of oscillator bandwidth. In electrotechnics it is known that the bandwidth $\Delta\omega$ depends on stored energy E_{Stored}, resonance frequency ω and power loss caused by damping E_{Loss}.

$$\Delta\omega = \omega\frac{E_{Stored}}{E_{Loss}} \quad (1)$$

This law from electrotechnics simplifies mathematics significantly. The hits from Brownian Movement are simply supplying the oscillator with the energy E_{Loss}.

Antigens can also be equipped with alpha-helices. Alpha-helices have non-linear spring characteristics. In this case a non-linear tensor differential equation must be solved for describing antibody-antigen interactions correctly.

Fig. 4 shows the differences of spectra for an undamped beta-sheet, a damped beta-sheet and an alpha- helix.

But it must be taken into account that the interaction between an antibody and an antigen is slightly different from the interaction between an antibody and a virus or a bacterium. So a mathematical analysis of a complete virus or bacterium makes sense. The rank of tensor differential equation depends on the number of epitops on the surface of the virus or bacterium membrane. A virus with 1500 epitopes requires a tensor differential equation of rank 1500, a bacterium with 1500000 epitopes requires a tensor differential equation of rank 1500000. If the epitopes have alpha-helices the differential equations are of non-linear type which becomes a mathematical challenge, but this type of mathematics is manageable.

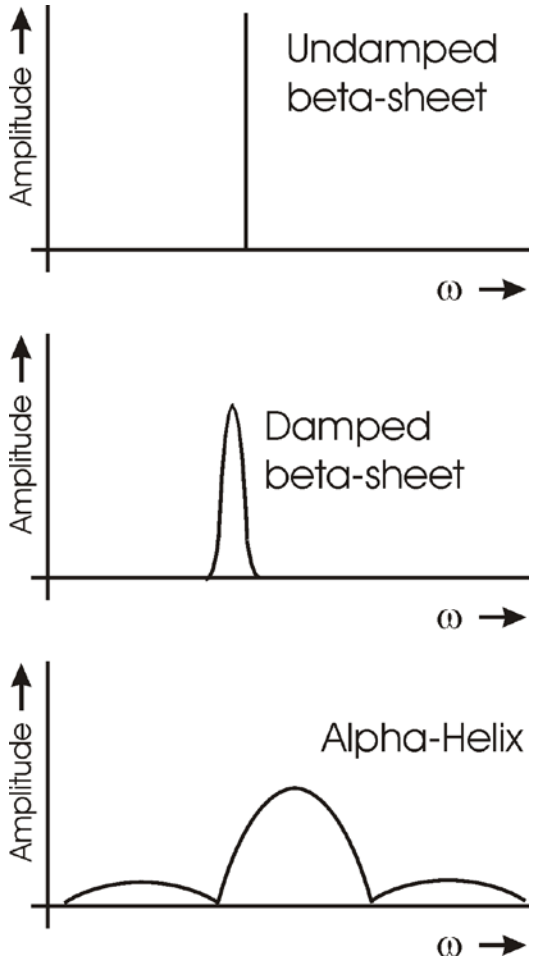

Fig. 4: Differences of the spectra of an oscillator with an undamped beta-sheet, with a damped beta-sheet and with an alpha- helix

Mathematical calculation of the interaction between antibody and cell is on a higher level, because there is an additional interaction between the alpha-helices of a cell membrane protein and the constant regions CL and CH1 of an antibody. Mathematical correlation leads to the assumption that MHC 1 is the responsible cell membrane protein with high probability. The interaction between the MHC 1 protein and the constant region CL/CH1 of the antibody can switch the antibody off. This is important for therapeutic antibodies against cancer cells. A normal antibody is from mathematical point of view not able to reach a cancer cell with working MHC 1 proteins, because the MHC 1 proteins are switching the antibody off.

Another important result of our mathematics is an explanation of autoimmune diseases. Normally the MHC 1-proteins on the cell surface are protecting the cell against antibodies. The MHC 1-proteins are interacting with the constant regions CL and CH1 of an antibody and switch the antibody off. A disturbed interaction leads to a defect in antibody switch off; the antibody becomes an autoantibody and attacks the cell. The cell will be destroyed by the immune system.

One example: Diabetes type 1 requires according to our electrodynamic binning theory a virus or bacterial infection focussed on beta-cells; otherwise Diabetes type 1 is not possible. After infection the immune system is producing antibodies with CL and CH1 constant antibody regions that are not able to interact correctly with the MHC 1-proteins. Now the alpha-helical MHC 1-epitopes of the beta-cells are not able to switch off the antibodies; the beta-cells will be detected as foe and destroyed. The same effect can have a too big number of MHC 1- proteins on the cell membrane; in this case the electromagnetic fields of neighboured MHC 1-proteins can interfere physically. Third party measurements have found that MHC 1 is involved in diabetes [33].

VII. ELECTRODYNAMIC BINNING THEORY AND PHAGE DISPLAY TECHNOLOGY

Phage display is currently used to create bio-molecular bibliotheca. Using our mathematics we found the following critical points.

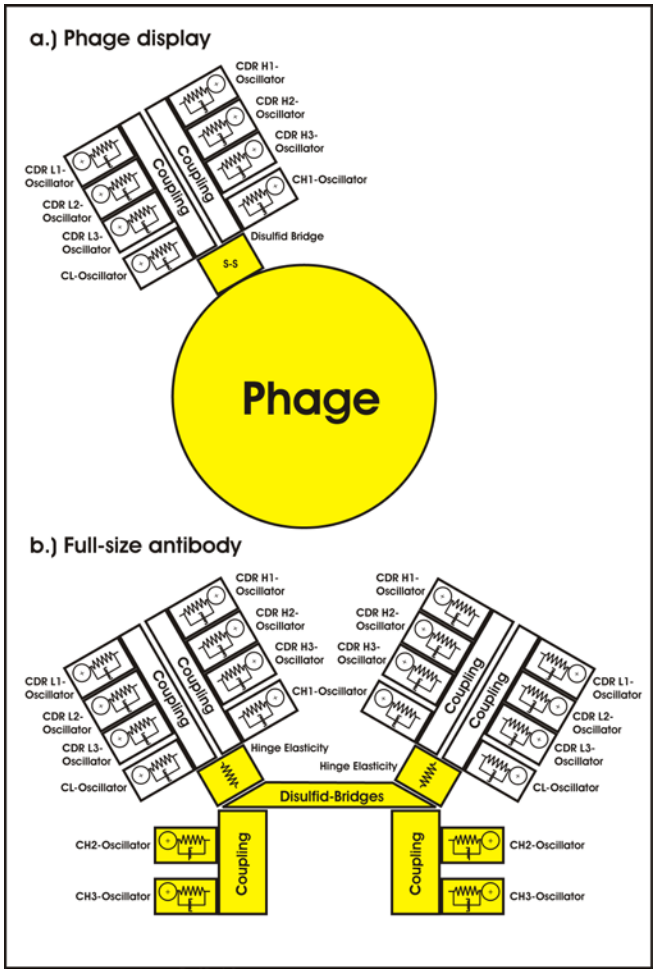

Fig. 5: Comparison of phage-display and full-size antibody. The masses of the phage and the constant regions of a full-size antibody are different (yellow). Additional to this the Phage does not have the hinge elasticity of a full-size antibody.

1. With phage display technology it is possible to produce broadband antibody components with limited specificity and affinity. The CDRs have slightly different affinities to different antigens. This is no problem if the antigen is of broad band type (damped beta-sheet or alpha-helix) but it can become a problem if the antigen has an undamped beta-sheet in his epitope. In this case affinity is not comparable with a natural high affinity antibody.

If for example a natural high affinity antibody can detect a big concentration of antigens in a distance of 2 mm, an antibody created with phage display has a detection range of only 1 micron in best case.

2. Transferring the binding sites from phages to complete antibodies reduces affinity according to our mathematics. The higher the affinity the higher is this effect. Physical reason for this is that a phage has a mass different from the mass of the CH2 and CH3 region. A high affinity phage Fab-fragment would theoretically lose its affinity and specificity completely (Fig. 6a), a real Fab-fragment partly (Fig. 6b). To compensate this effect normally the CDR-H3 is modified. Modifying only CDR-H3 leads to an increase of affinity, but CDR-L1, CDR-L2, CDR-L3 have still affinity to a slightly different antigen, and CDR-H1 and CDR-H2 can change their affinity to a different antigen. This can lead to harmful side effects. Even a process of sequential change of all CDRs will not lead from mathematical point of view to a high affinity antibody that is comparable with a natural high affinity antibody. The reason for this is that the beta-sheets from phage display have always damping.

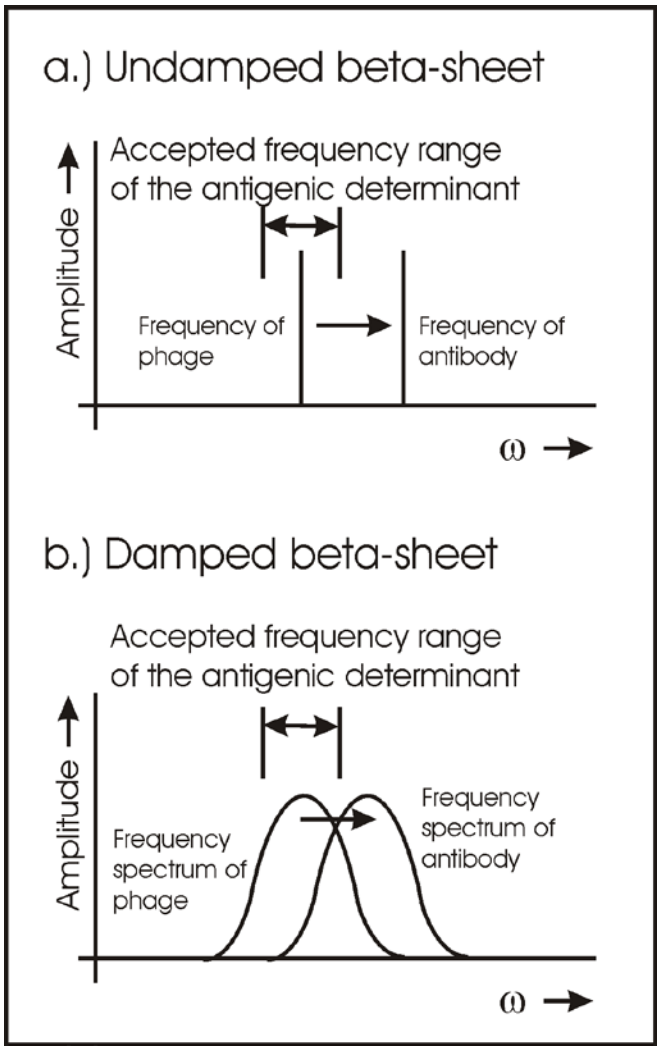

Fig. 6: Frequency change of Fab-oscillators caused by Fab-transfer from phage to full-size antibody. A Fab-fragment with undamped beta-sheets would loose affinity totally (a); a Fab-Fragment with damped beta-sheet shows a decrease of affinity and specificity (b).

So we think it is not possible with phage display to produce therapeutical antibodies that have effectivity comparable with natural high affinity antibodies. Additional to this harmful side effects are possible. Taking a known high affinity antibody and modifying all CDRs according to mathematical laws will lead theoretically to significantly better results. In this case an antibody without beta-sheet damping can be produced.

VIII. CONCLUSION

Based on own and third party measurements we calculated that there is no chemical binding/binning between antibody and antigen with a probability of 99.999997% as it is expected from the induced fit theory. Instead of this there is electrodynamic binning with a probability of 99.9999999%. That means the dogma that the constant region of an antibody has no influence on the binning of an antibody is no more sustainable. From this it follows that the dogma of a chemical binding/binning between antibody and antigen is also no more sustainable. This has an extreme impact on the development of therapeutic antibodies. In combination with our theory of autoimmune antibodies which will be published soon there are the following impacts for the design of therapeutic antibodies.

1. Designing therapeutic full-size antibodies with help of phage display will lead in general to antibodies with low affinity. Affinity maturation by modifying only CDR-H3 can lead to harmful side effects. Other technologies are required to produce high affinity antibodies without creating side effects.
2. Natural full-size antibodies against cells (for example cancer cells with working MHC 1 proteins) will not work because cells are inactivating antibodies about 3 nm before reaching the cells.
3. Camelid antibodies or comparable antibody technologies can reach cancer cells, but the effectivity of this antibody type compared to a full-size antibody is very small, because this antibody has no motor.
4. Antibodies with linked toxophores are not able to bind to cancer cells with working MHC 1 proteins and their long distance detection system is not working. They stop in a distance of 3 nm to the cell. By stochastic effects the toxophore can reach the cancer cell. This type of antibodies will not work in solids.
5. Theoretically it is possible to created special antibodies that are able to attack all cancer cells in liquids and solids with high effectivity.
6. Vaccines against cancer will not work, because the antibodies produced by the immune system will not bind to cancer cells with working MHC 1 proteins, they will stop 3 nm in front of the cancer cell.
7. There is a chance to reduce the effectivity of autoantibodies with personalized molecules by a factor of 250000 in liquids. Autoantibodies with reduced effectivity are not able to move in solids.

Currently development of therapeutic antibodies is based on some experimental findings and a try and error process;

other experimental findings as the contribution of the constant regions to affinity and specificity are ignored completely. So development of a working therapeutic antibody is an extreme risky process.

Mathematics in combination with electrodynamic binning theory can help in installing a controlled engineering process for development of therapeutic antibodies with significant lower risk.

We think that electrodynamic interaction is a general principle of life.

REFERENCES

U. Riss, *Theory of long distance interaction between antibodies and antigens*, European Biophysics Journal, Vol. 40, No. 8, 2011, pp. 987-1005

D. E. Koshland, *Application of a Theory of Enzyme Specificity to Protein Synthesis*, Proc Natl. Acad. Sci. U S A 44, 1958, S. 98-104

S. Sheriff, E. W. Silverton, E. A. Padlan, G. H. Cohen, S. j. Smith-Gill, B. C. Finzel and D. R. Davis, *Three-dimensional structure of an antibody-antigen complex*, Proc. Natl. Acad. Sci. U S A. 1987 November; 84(22): 8075–8079.

Y. Chen, *Generation and Affinity Maturation of Fully Human Soluble V_h Domain Antibodies and IgGs using dsDNA Display*, Bit's 4th Annual Congress of Antibodies, Peking, 2012

A. Rothen, *Immunological Reaction between film of antigen and antibody molecules*, JBC, 1946

U. Riss, *Theory of Affinity Maturation of Antibodies*, Advances in Bioscience and Biotechnology, 2013, 4, 67-72

P. J. Hudson and A.A. Kortt, *High Avidity scFV Multimers, Diabodies and Tribodies*, Journal of Immunological Methods, Vol. 231, No 1-2, 1999, pp. 177-189

Kato K, Matsunaga C, Odaka A, Yamato S, Takaha W, Shimada I, Arata Y, *Carbon-13 NMR study of switch variant anti-dansyl antibodies: antigen binding and domain-domain interactions*, Biochemistry 1991; 30:6604-10

N. McCloskey, M.W. Turner, P. Steffner, R. Owens, D. Goldblatt, *Human constant region influence the antibody binding characteristics of mouse-human chimeric IgG subclasses*, Immunology, 1996, 88, 169-173

Otto Pritsch, Gilbert Hudry-Clergeon, Malcom Buckle, Yves Petillot Jean P. Bouvet, and Jean Gagnon, *Can Immunoglobulin CH1 constant Region domain modulate Antigen binding affinity of Antibodies?*, J. Clin. Invest, Volume 90, Number 10, November 1996, 22352243

Marcella Torres and Arturo Casadevall, *The immunoglobulin constant region contributes to affinity and specificity*, Trends in Immunology, Vol. 29, No. 2, 2008

Arturo Casedevall and Alena Janda, *Immunoglobulin isotype influences affinity and specificity*, PNAS, Vol. 109, no. 31, 2012, 12272 -12273

Marvela Torres, Narcis, Fernandes-Fuentes, Andras Fiser, and Arturo Casedeval, *The immunoglobulin heavy chain constant region affects kinetic and thermodynamic parameters of antibody variable region interaction with antigen*, Journal of Biological Chemistry, Volume 282: 13017-13927 Number 18, 2007

Tudor D. et al. (2012) *Isotype odulates epitope specificity, affinity, and the antiviralactivities of the anti-HIV-1 human broadly neutralizing 2F5 antibody*, Proc. Natl. Acad. Sci. USA 109: 12680-12685

Cooper LIN, et al. (1993*) Role of the heavy chain constant domains in antibody-antigen interaction. Apparent specificity differences among streptococcal IgG antibodies expressing identical variable domains*, J Immunol 150: 2231-2242

McLean GR, Torres M, Elguezabal N, Nakouzi A, Caseval A 2002) *Isotype can affect the fine specificity of an antibody for polysaccharide antigen*, J Immunol 169: 1379-1386

Torosantucci A, et. Al. (2009) *Protection by anti-beta glucan antibodies is associated with restricted beta 1,2 glucan binding specificity and inhabitation of fungal growth and adherence*. PLoS ONE 4:e5392

Xia Y, Pawar RD, Nakouzi AS, Herlitz L, Broder A, Liu K, Goilav B, Fan M, Wang L, Li QZ, et al. *The constant region contributes to the antigenic specificity and renal pathogenicity of murine anti-DNA antibodies*,J. Autoimmun 2012; 39:398-411; P

Hubbard MA, Thorkildson P, Kozel TR, Aucoin DP. *Constant domains influence binding of mouse-human chimeric antibodies to the capsular polypeptide of Bacillus anthracis*, Virulence 2013; 4:483-8

Kozel TR, Murphy WJ, Brandt S, Blazar BR, Lovchik JA, Thorkildson P, Percival A, Lyons CR. *mAbs to Bacillus anthracis capsular antigen for immunoprotection in anthrax and detection of antigenemia*, Proc. Natl. Acad. Sci. U S A 2004; 101:5042-7

Beenhouwer DO, Yoo EM, Lai CW, Rocha MA, Morrison *SL. Human immunoglobulin G2 (IgG2) and IgG4, but not IgG1 or IgG3, protect mice against Cryptococcus neoformans infection*, Infect Immun. 2007; 75:1424-35

Andrea Nova, Sinan Keten, Nicola M. Pugno, Alberto Redaelli, Markus J. Buehler, *Molecular and Nanostructural Mechanisms of Deformation, Strength and Toughness of Spider Silk Fibrils*, Nano Letters 10 (7), 2626-2634, 2010.

Keten, S. and M.J. Buehler, *Nanostructure and molecular mechanics of dragline spider silk protein assemblies*. Journal of the Royal Society Interface, 2010., published online June 2, 2010

Sinan Keten, Markus Buehler, *Atomistic Model of the Spider Silk Nanostructure*, Applied Physics Letters 96, 2010.

S. Keten, Z. Xu, B. Ihle, M. J. Buehler, *Nanoconfinement controls Stiffness, Strength and mechanical Toughness of β-Sheet Crystals in Silk*, Nature Materials, 2010, 9, p. 359-367.

A. Idris, M. T. Alam and A. Ikai, *Spring Mechanics of alpha-helical Polypeptides, Protein Engineering Design and Selection*, 13, 763-770, (2000)

Toshihiko Kiwa, Akira Tenma, Kenji Sakai, and Keiji Tsukada, *Label free immune assay using terahertz chemical microscope*, IMCS 2012 – The 14th International Meeting on Chemical Sensors

Peter Ortoleva, http://www.photonics.com/Article.aspx?AID=54944

Peter Ortoleva, http://phys.org/news/2013-09-bug-virus-detection-technology.html

Kahn, http://www.youtube.com/watch?v=R3LxbADWTFU

L. Montagnier, J., Aäissa, J *et al*, *Electromagnetic Signals are produced by aqueous Nanostructures from bacterial DNA Sequences*, Interdisciplinary Sciences: Computational Life Sciences, 6 January 2009, Volume 1, Number 2, 81–90

L.Montagnier, J. Aäissa, *et al*, *Electromagnetic Detection of HIV DNA in the Blood of AIDS Patients treated antiretroviral Therapy*, Interdisciplinary Sciences: Computational Life Sciences, 3 July 2009, Volume 1, Number 4, 245–253

Emma E. Hammilton-Wiiliams, Stephanie E. Palmer, Brett Charlton, and Robyn M. Slattery, *Beta cell MHC class I us a late requirement for diabetes*, PNAS (2003), 6688-6693