hello everyone my name is Ben myum from

Science Center and well talk about the

pharmacokinetics and

pharmacodynamics of therapetic proteins

now part

five the goals of this section are to

appreciate the ability of their itic

proteins to trigger an immune reaction

to differentiate nonneutralizing

neutralizing and crossreactive anti drug

antibodies and the effect on PK and

PD to understand the effect of clearing

versus sustaining any drug

antibodies to recognize any drug anybody

interaction as a possible clearance

pathway for therapeutic

products immunogenicity is the

capability of a substance to elicit an

immune response so most therapeutic

proteins um as protein drugs are

immunogenic and may stimulate the

patient immune system to form socalled

antidrug antibodies or

Ada that may inactivate the therapeutic

effects of the protein

drug there are a variety of theories

what triggers the formation of any drug

antibodies especially if they

administered therapeutic protein is an

endogenous molecule or some that is

highly similar to an endogenous

molecule one of the dogmas that uh is is

uh used is that protein aggregates are

immunogenic so Aggregates are being

recognized as the main driver of an auto

reactive response to human theraputic

proteins usually in the body

uh proteins are only available in

monomeric form and the the idea is that

monom if monomeric proteins are

administered to a patient even after

repeated Administration you would have

immune tolerance to those uh molecules

as uh they are recognized as um an

endogenous molecule and by that would

not have um an immune reaction however

once these monom generic proteins form

an aggregate then this aggregate may be

recognized as a potential Hazard for the

body and may trigger a Breaking of the

immune tolerance and the formation of

antidrug

antibodies the ability of an antigen to

induce an Adaptive immune response can

have a variety of different factors that

are modulating um of course con

contaminants and impurities may play a

role uh as I mentioned the Aggregates

and the formulation that ultimately to

determine the number and the

availability of Aggregates uh may play a

role the route of Administration has

been discussed as a potential Factor uh

for some therapeutic proteins that seem

to be higher incidence of ADA formation

after subcon compared to intervenous

Administration

um some thoughts about that uh are the

potential of the formation of immune of

of Aggregates after subcutaneous

administration at the injection site

that may ultimately trigger then this

increased immune uh reactivity uh there

are also other factors that have been

discussed like the dose level the

lengths of therapy uh genetic factors in

uh individual patients especially the H

type has been discussed and there are

many limitations with regard to

comparability of immunogenicity data

based on the essay technologies that are

used to assess anti drug

antibodies if we talk about anti drug

antibodies uh we have to differentiate

between neutralizing and

nonneutralizing any drug antibodies

nonneutralizing Ada bind to the

therapeutic protein but do not interfere

with its ability to bind to the Target

structure so the the theraputic protein

can still maintain its activity even

though an ADA molecule is bound to it in

contrast to that neutralizing any drug

antibodies bind to or near the target

binding domain of the therapeutic

protein and by that interfere with its

ability to bind the target

receptor a specific form of neutralizing

any drug antibodies are socalled cross

reative any drug anti bodies those are

the ones that do not only bind to the

biological therapeutic so the

therapeutic protein that has been

administered but also to its

endogenous analog or homologue that

corresponds to that dioptic protein an

example for that where this had the

Fatal consequences was a socalled epre

case where a uh arthop potin uh

medication was administered to patients

uh that uh arthop potin um was uh had a

change in the production process in the

packaging material actually uh that uh

ultimately resulted in want some

patients to produce a condition

called uh anti arthropo and anybody

mediated who pure Red Cell aasia so

basically these patients formed cross

reactive any drug antibodies not only

against the arthop potin that was in the

eprx medication but also against the

endogenous arotin that was produced by

those patients and by that they could

not form red blood cells anymore so

crossreactive Ada is very much a concern

and is especially relevant for those uh

therapetic proteins that are uh

replacing um endogenous

molecules uh like grow factors or

enzymes in enzyme replacement

therapy what happens to uh the immune

complexes that are formed when any drug

anybodys bind to therapeutic proteins

so the body uses the same

uh elimination processes as for any

other immune complex thats formed so

they trigger the regular elimination

process which is uptake and lysosomal

degradation by the reticular endothelial

system so fosic cells like monocytes and

macrofagos that ultimately recognize

these immune complexes take them up and

degrade them to amino acids that occurs

primarily in liver and spleen but is

mediated by FC gamma receptors

another FC receptor that we have not yet

talked about an FC gamma receptor that

basically

recognizes another binding site on the

ofc domain of the anti drug anybody

primarily FC gamma

R uh human platelets contribute to the

clearance of IG containing uh complexes

as they also Express this receptor and

bind uh IGG complexes that and then are

internalized the platelet as well as a

complex in circulating uh

fyes so what are the potential effects

of ADA formation with regard to

pharmacokinetics and

pharmacodynamics so as we mentioned you

can have neutralizing Ada or

nonneutralizing Ada independent of

whether they neutralizing or

nonneutralizing they can have both a

effect on the clearance of the

theraputic protein based on the fact

whether the formed immune complex

triggers the natural endogenous

elimination

process if that process is triggered

then we have an increase in the

clearance of the therapeutic protein

shown either here or here and we have a

socalled clearing any drug antibody

which results in reduced exposure and

reduced activity

in some instances we can have the

opposite that the immune complex

actually stabilizes the theraputic

protein and then we have a socalled

sustaining antidrug antibody so lets first talk about the clearing antidrug antibody those antibodies bind to the drug and alter its phic kinetics by increasing the clearance reducing the systemic exposure and decreasing the distribution to Target organs so the you the formed immune complex between the Ada and the uh thetic protein trigger the reticular endothelial system and ultimately constitute an additional elimination pathway thereby reducing the elimination halflife of that compound an example how this looks like is shown on the right s for a monocon antibody that has been given here in uh for weekly doses indicated by the arrows on top for different weekly doses the red line shows what happens with regard to concentration time profile in individuals that have no Ada formation so they are Ada negative you see a nice build up of the systemic exposure uh of uh that results from these four doses of the antibody in contrast to that the same dose is given

to individuals that now have the

formation of any drug anybody see that

initially you get very similar exposure

once the Ada formation kicks in after

one to two weeks you basically get a

rapid uh reduction in systemic

exposure vastly increased clearance for

this specific therapeutic protein and by

that of course you have reduced systemic

exposure and by that likely uh lack or

loss of efficacy of this

treatment the sustaining antidrug

antibody um as I mentioned before also

forms immune complexes by those

complexes based on their size their

shape their charge do not trigger

regular endogenous alumination fores but

serve as a storage Depot for the

therapeutic protein by that reduce the

clearance of the drug and result in a

prolonged systemic exposure and

increased distribution to Target organs

the half lifee of the therapeutic Pro uh

protein often approaches in those cases

the halflife of the Ada so the immune

globulin Le this is often observed for

small prod Therapeutics like cyto or

hormones uh where the immune complex

formation then

stabilizes the molecule and by that

extends its half line its possibly also

mediated through FCI and mediated

recycling because now you have uh the

Ada molecule that can serve as the the

uh driver for this recycling process

with an intact FC

fragment so Ada is ultimately an

additional element clearance paway for

therapeutic proteins thats shown again

here with our two compartment model

typical for pH the two compartment

pharmacokinetic model for therapeutic

protein we can have as we discussed

presystemic degradation we have

protolytic degradation for the those

molecules that are small enough can have

that can undergo glome filtration they

may undergo renal metabolism we talked

about FC in recycling and about Target

mediated drug disposition as a potential

elimination pathway and now in addition

to that we have the antidrug antibody

uh formation the immune complex
formation and ultimate uh removal and
degradation of this Ada drug complex as
an addition
clearance pathway that needs to be
considered for therapeutic
proteins so in summary for this section
therapeutic proteins May elicit an
immune response in individual patients
that may lead to the formation of any
drug antibodies numerous factors play a
role in this process including
Aggregates of the therapeutic protein
Ada may be neutralizing or non
neutralizing independent of their
neutralization status they may also have
a clearing or syst in effect on the PK
of the therapeutic protein clearing ad
effects are a frequent cause of
therapeutic failure in longterm therapy
with therapeutic
products again now a self assessment
question that summarizes some of the
concepts in this
section for those interested in further
reading there is a list of uh textbooks

and Publications that might be of

interest for you that highlight and

summarize uh some of these Concepts

again in a bit more

detail thank you for your

attendance