hello everyone my name is Ben myum from
Science Center and I will uh provide you
some uh insights on the pharmacokinetics
and pharmacodynamics of therapeutic
proteins now part three
the goals of this section are to
recognize the effect of major
elimination processes on the disposition
of theraputic
proteins to understand the concept of
Target mediated direct disposition and
its impact on the pkpd of many
therapeutic
proteins and to appreciate the impact of
renal and hepatic impairment on the
disposition of therapeutic
proteins theraputic proteins undergo the
same catabolic Pathways as endogenous or
dietetic proteins and that means that
they are degraded to amino acids as
their building blocks that are
reutilized in the endogenous amino acid
pool this protolytic degradation occurs
in a variety of different organs and
tissues major sides of protein

degradation are

the gastrointestinal tract the skin the

muscle and the reticular endotherial

system the main contributors are indial

cells of that facil that um use the

process of

endocytosis to take up vesicles with

theraputic proteins and then

subsequently process those vesicles and

degrade the proteins within them andal

cells obviously line uh blood vessels

throughout the body uh and the overall

surface area towards uh the blood

vessels is more than a th000 square

meters in adult human so even though the

endocytosis process itself is relatively

slow and

inefficient this is offset by the large

surface area thats available to

facilitate that

process that means that those organs and

tissues that have large capillary bands

with many endothal cells are major

contributors to the

overall degradation of the apic proteins

and these are the skin the intestine and

muscle

tissues in addition to that the

reticular endotherial system so

monuclear fosic cells like macrofagos

monocytes ker cells lahan cells and

others are a major contributor to

protein degradation by taking up

theraputic proteins again uh through

vesicles into their

uh in these cells and ultimately the

processing of these vesicles to degrade

the therapeutic prods that included in

them my minor sites of degradation are

also the liver the kidneys the spleen

and the lungs but for specific

therapeutic proteins some of these

organs may be a major

contributor the main prerequisite for

protic degradation is intracellular

uptake there are a variety of processes

how this can be

facilitated the most basic one is called

pinocytosis which is a fluid phase

endocytosis and the main process that

endothelial cells use to take up theic

products there are also receptor

mediated endocytotic processes either by

unspecific or by Target receptors

unspecific receptors or promiscuous

membrane receptors like the LDL receptor

or sugar recognizing receptors like the

Manos or the fucos receptor that can

recognize certain structure features in

therapeutic proteins uh and by that

facilitate the endocytotic

uptake of uh those

molecules Target mediate endocytosis is

then The Binding to the pharmacologic

Target receptor for example a membrane

standing receptor that can then be

internalized with the theraputic protein

uh receptor complex and this complex can

then

internalized and further processed in

the cell and ultimately lead to the

degradation of the theraputic

prod Target mediated drug disposition is

one feature that many therapeutic

proteins

exhibit and that is basically the

interaction with the target receptor

that then also contributes an

elimination process so this is

symbolized here in this little graphic

where a pharmacokinetic two compartment

model is shown where you have protic

degradation from either of those

compartments you can also have renal

metabolism well talk about that in a

second and in either of these

compartments the uh therapeutic parin

can now interact with its Target

receptor and of course Target receptors

also have a a turnover kinetics have a

specific synthesis and degradation rate

that ultimately uh influence and Define

the Dynamics of this whole process now

once the therapeutic protein and the

receptor interact you get the uh

receptor uh protein complex that

ultimately drives the effect this is

usually defined by binding kinetics

within K on and a k off

process all this is similar to what we

are familiar with for small molecule

drugs the major difference now is that

this drug receptor complex or

therapeutic protein receptor complex can

be inter internalized in the Target cell

and can

undergrow losal degradation and by that

you not only have a receptor interaction

thats reversible but now you also have

a

unidirectional elimination

process so receptor interaction

contributes substantially in this case

to the overall clearance and by that the

disposition of the therapeutic protein

and since usually the target receptor is

only available in a finite number on the

molecular

level you can easily saturate that

elimination process and the consequence

of that is a nonlinear pharmacokinetic

Behavior

so Target receptors are usually High

Affinity low capacity binding size they

saturable at low molar ratios between

the protein and the receptor and that as

I mentioned leads to dose dependent

nonlinear phac kinetic Behavior an

example for that is a macras colony

stimulating factor which is eliminated

by two parallel elimination

processes one is a line a linear renal

metabolism process and the second one is

a receptor mediated uptake into macras

so mcroof fases Express the

pharmacologic target receptor for mcsf

mcsf binds to that the target receptor

mcsf complex is internalized and under

goes uh then losos of

degradation since there is only a finite

number of receptors on macro phases

available you basically get with

increasing uh Doses and increasing level

of saturation of that elimination

process and thats shown in the graphic

on the right side for three dose levels

0 one and 0 millgram per kilogram you

see at the lowest dose level a very

rapid decline in the

concentration since both elimination

Pathways the linear metabolism as well

as the receptor mediate process are

fully active so this is below the

saturation level of the receptor

mediated

process when you go to higher doses you

start to saturate to overwhelm the

available

receptors uh so the receptor mediated

process gets to a saturation level the

extreme is shown here at the highest

dose level where you have now a much

flatter curve a much uh

less uh or much slower decline in the

concentrations as now the process is

largely only U mediated by the renal

elimination Pro renal elimination

process so the Met metabolism of of mcsf

but not by the receptor mediated process

once you get to concentrations that are

low enough to get out of that

concentration range now the

secondary parallel receptor mediated

elimination process kicks in and you

have the rapid decline in the

concentrations so this is a typical

behavior that many therapeutic proteins

exhibit in a slightly different fashion

uh this dose dependent clearance is now

shown here in this graphic on the y AIS

the clearance of the theraputic protein

on the xaxis the concentration in a

logarithmic scale

now again I use a

simple two compartment pharmacokinetic

model with two parallel elimination

Pathways one through unspecific

protolytic degradation thats nons

setable or what I call it catabolic

clearance and then a second one thats

receptor mediated and the receptor

mediated process can be

um conceptualized in a variety of

different different ways uh one

simplified way is shown here where it is

simply expressed as a with mikis men

type kinetics as a curable clearance

pathway with a km value that uh

indicates the concentration at

0 of the maximum elimination and Vmax

the maximum elimination

speed and then the expression is shown

here where the total clearance

is the sum of the nons setable catabolic

clearance and the setable target mediate

elimination

passway conceptualized here as Vmax

divided by the sum of KM and the

concentration of the

drug so now in the graphic you see the

contribution to the overall clearance

the overall clearance is shown in in

blue um this has two components the

cabol clearance in purple the purple

dash line which is independent of the

concentration but is at a low level so

remains at this level and then the

second pathway the receptor immediate

one a high clearance level at very low

concentrations once you get into a value

around km with the concentration of the

drug you get into the saturation range

and ultimately you can completely

saturate that uh clearance process in

the sum of that is then uh the blue

curve as shown here so a high

concentration dependence of the

clearance process depending on what kind

of dose you give and what kind of drug

concentration is still remaining in the

body thats a typical behavior that we

experience with a lot of therapeutic

proteins and that is shown in a graphic

here for typical nonlinear fic kinetic

behavior for monoclonal anybody that is
given every two weeks so you see the
concentration time profiles that result
from administration of either 00 0
00 0 00 and 00 millgram every
two weeks when you get to concentration
levels that are much higher than the km
value or much higher than the saturation
level for the Target minut elimination
process you have nearly linear
pharmacokinetic Behavior thats shown
here for the three highest
doses once you get to concentrations at
the lower doses where you get out of the
saturation range for the Target mediate
process you get very rapid elimination
at lower concentrations and that is
shown here in the drop especially of the
light green curve uh at the end of each
dosing interval so phac nonlinear
pharmacokinetic Behavior due to Target
mediated drug
disposition now the kidneys uh can also
contribute to the elimination of um
therapeutic proteins but not as for
small molecules by excretion but rather

than by metabolism so therapeutic

proteins are usually not excreted in

unchanged form in urine and if that

occurs this is usually a pathologic

condition

so uh the kidneys however can be a major

site of protein metabolism for smaller

proteins that undergo glomera

filtration now glome filtration is a

rate limiting step and theres a size

selective cut off of approximately 9

kilodalton although the effective

molecular radius based on molecular

weight and Confirmation is probably more

important and the limiting factor rather

than the real molecular weight uh for

the molecule

so glal filtration is most efficient if

molecular weights are below 0 kilon it

reaches for very very low molecular

weights the GL the um GL filtration rate

uh but at higher concentrations the

filtration rate uh sharply falls off and

has then this absolute cut off of around

uh 9 kilol theres also a certain

charge selectivity in addition to the

size selectivity that may play a role

the consequence of that is that

therapeutic proteins that are small

enough to under GL GL filtration into

the primary urine so the proximal

tubulus in the filtrate and now they can

undergo either in luminal

metabolism through peptidases in the

brush border

membrane uh and then the resulting amino

acids and and small uh peptide fragments

can be taken up by peptide Transporters

to especially pepti or lesser degree

pepti and can be reutilized in the

endogenous amino acid

pool

for

larger peptides and proteins that are

still small enough to underg go glom

filtration like interin interin

gross hormone or insulin they basically

have are filtered into the proximal

tubular tub

and are then taken up in these proximal

tubular cells by

endocytosis and undergo losal

degradation again bleeding to amino acids that can be reutilized in the endogenous pool theres also a third process that had been described peritubular extraction so direct uptake from the blood vessel either by receptor nonreceptor mediated uh uh processes uh which uh can contribute to the ele to the metabolism of therapeutic proteins like Ron and Insulin but usually its only a minor elimination pathway so what does this then mean clinically with regard to patients that have renal impairment for protein drugs with a molecular weight of uh below the cut off of 0 to 9 kilodalton right here 0 Ive had 9 on the previous slide there obviously as I mentioned before not an absolute cut off in in weight but basically uh the uh hydrodynamic radius is more important uh for regulatory purposes the Food and Drug Administration usually uses the molecular weight of albumin with 9

kilodalton as abum is known to be not

filtered uh by gloma

filtration so for therapeutic proteins

that are smaller than this cut off they

are expected to be affected by renal

impairment there are examples out there

that the show this very nicely one is

shown here thats Rec combinant human

interlan 0 which a molecular weight of

kilton so its below the cut off is

filtered and what you see here are

concentration time profiles of uh

interlan 0 in patients with uh

decreasing renal function measured as

creatinine clearance so either normal

renal function nucle larger than 0 m

per minute per square meter and then

then uh successively reduced uh renal

function you see with reduced renal

function you get an reduced clearance

and increased systemic exposure in an

increased halflife of these therapeutic

products so what happens then on the

Other Extreme which therapeutic proteins

which have a molecular weight thats

larger than the cut off of 0 or 9 uh

kilodalton they are expected to be
unaffected by real impairment uh monocon
antibotics for example with a molecular
weight of 0 kilon are not filtered and
by that are not expected to be affected
by renal impairment an example is shown
here with Lusa map that has been uh
investigated in patients with normal
renal function uh shown here has a solid
line compared to individuals with either
severe renal impairment with a CR
clearance below 0 Millers per minute or
with in patients with endstage renal
disease and as you can see the systemic
exposure is very similar in those three
groups there were no uh relevant
differences in AU and cmax between these
groups and by that no effect on real
impairment on anybody disposition uh was
uh observed Obed in this specific
publication now when we since we talk
about uh organ impairment uh we probably
should also mention hepatic impairment
so uh hepatic impairment similar to uh
real impairment for uh those compounds
that are larger than 9 kilodalton atic

impairment also has no impact for most

therapeutic proteins the liver is a

major site of

of protein metabolism for some larger

proteins as I mentioned before can be an

important contributor in in some

specific cases studies in hepatic

impairment patients are however rarely

performed in drug development for

therapeutic proin since hepatic

metabolism is for most of them not the

major elimination pathway and no

regulatory guidance by FDA is uh

available Beyond General recommendations

however uh the colleagues at FDA uh put

together uh a nice publication in 00

where they collected data for uh

theraputic proteins from their databases

mostly monoclonal antibodies and they

could show that in of them there was

no effect of M to moderate hepatic

impairment on the phac kinetic that

would require those adjustments however

there were a few exceptions and three of

them there was actually a reduction in

the uh system exposure the a see by

to 0 so its basically the opposite of

what you usually expect for small

molecular drugs where peretic impairment

of it oftentimes results in an increase

in the systemic exposure in this case it

was a decrease in the systemic exposure

its potentially related to concurrent

hyper globulinemia in atic impairment

via saturation of the socalled FC uh RN

or neonatal FC receptor uh process that

well talk about in uh the next

section theres also case report that I

think makes the point very well for Pine

tumor map which has been used

specifically uh for the treatment of a

patient with metastatic coloral cancer

that had

um hepatic impairment uh child food

Class B due to liver metastasis and

while small molecule drugs in this

specific scenario could not be used

anymore due to this hepatic impairment

it was specifically this patient was

specifically mve to a therapy with pen

Tumo map as a cross

wal um anti or a a anti egfr drug for

cross wild type metastatic coloral
cancer the drug was well tolerated and
the concentration time profile observed
in this specific case report was very
comparable
to what historic data showed uh in housy
individuals this concludes the sessional
elimination processes for theraputic
proteins in summary unspecific protic
degradation is the major elimination
pathway for most theraputic proteins and
is facilitated by endotherial cells and
the reticular endothal system Target
Media direct disposition may be a major
contributor to the elimination of the I
prots at low molar concentrations
relative to their target abundance and
often results in nonlinear phic kinetic
Behavior plastic elimination organs for
small molecule drugs like liver and
kidneys are only minor contributors to
the elimination of most therapeutic
proteins and renal metabolism May
contribute to the elimination of
proteins with a molecular weight below
9 kilodalton that undergo glom

filtration and real impairment May

reduce the clearance of these

proteins again there are two self

assessment questions for this

section