hello everyone my name is Ben M from the Center and well talk to you about the phac kinetics and pharmacodynamics of theraputic proteins now in part four the goal of this section is to understand the role of the neonatal FC receptor also termed fcrn in the disos disposition of anybody derived therapeutic proteins shown here is the typical structure of an immune globulin G molecule which has this wise shaped structure where you have two light chains and two heavy chains that are connected through the dulite bridges and you have have two antigen binding sides on the ends of these molecules on one side and you have a constant domain or FC domain on the other side on the FC domain there are a variety of different binding sites that are specific for the interaction with um socalled FC receptors and one of the FC re receptors we want to focus on is the neonatal FC receptor fcrn even though

its called the neonatal FC receptor is

equally expressed in adult individuals

and not limited to uh

neonates the neonatal FC receptor can

interact which with its specific binding

site on the FC domain of antibodies and

that includes monocon antibodies as well

as anybody derivatives that have an

intact FC

fragment and um the process works that

way that

[Music]

when

molecules thetic proteins from the

bloodstream this the vascular space here

and this is the intracellular space in

endal cells or

monoy when a vesicle is formed in the

membrane

by this pit then

this vesicle can include the fluid from

the vascular space which includes

therapeutic proteins like itg molecules

endogenous ones as well as monoclone

antibodies for example but also other

therapetic proteins here symbolized in

yellow once this vesicle is

formed is moved and processed in the

cell it is usually

acidified with an pH of approximately

six and in that

process

um

The Binding site on the ofc domain of

anybody can bind to the neonatal FC

receptor fcrn and fcn is shown here its

basically a membrin standing uh

heterodimer that ultimately is included

in this membrane theres no binding

Affinity at pH

but once the endosome is acidified

uh the fcn can bind to the specific

binding site on the FC

domain the consequences of that is that

now this fcrn anybody complex can be

sorted out into sorting complex and then

into Recycling endosome and can be

produced can be transported back to the

soul

surface where once the vesicle is open

up and the pH is adjusted to since

this was a pH dependent binding theres

no binding Affinity at pH so the

anybody is released out of The Binding

uh to FN and its basically recycled in

contrast to theraputic proteins like the

ones shown here in yellow that basically

do not interact with fcrn they undergo

Lal

degradation so this fcrn mediated

recycling process is an

efficient uh process to prevent IG

molecules from undergoing lososo

degradation the consequence of

that is that you have a substantially

increased resonance time and

substantially increased elimination half

life for HD molecules compared to other

similarly sized uh proteins in the body

the half life for IG two and four are

native lay around the to days igg

has a lower binding Affinity to FC and

by that the recycling process is less

efficient and by that it molecules have

a half life of approximately seven days

and if you give for example a murine IG

molecules to a human that has a very low

binding Affinity um to uh fcrn you have

a half five of one to two

days now the FC recycling process even

though it is an interaction of an a

therapeutic protein with a receptor is

usually not setable at therapeutic

concentration at which most monoclonal

antibodies or other uh theraputic

proteins that have a um FC domain and by

that a binding site to this receptor uh

at doses that that these molecules are

used

at the efficiency of this process is

shown in this little graphic where you

have um in plasma usually a

concentration of approximately Mill

gr per milliliter of IGG molecules so um

immune globulin G

endogenously of that

is every day newly synthesized but

is actually taken up into for

example endothelial cells or reticular

endothelial system cells for catabolism

now of that are recycled so thats

through the FC recycling process and

then only is actually

degraded now this recycling process is

not only limited to ig molecules but it

also includes albumin so albumin

molecules also have a specific binding

site for

fcrn by that can be also be recycled and

that fcn recycling uh of abum is also

the reason why abum has a relatively uh

long residence time and uh long halflife

in the systemic

circulation the recycling process for

albumin is shown here are taken up

every day for for degradation only

onethird is recycled and two are

degraded uh so the recycling process is

less efficient for abuan as it is for

itg

molecules now coming back to the

question of uh potential saturation of

this process what is shown here on the

left side is the relationship between

serum IG

concentrations and halflife and you see

that at the normal IGG concentration of

uh grams per liter uh we are right

where the arrow points here we are um at

so that results in a half life of

approximately days so this is the

solid line is the line for igg and

four with the whereas the dash line is

for ig with a lower binding Affinity so

if we only focus on the solid line then

were right here at in a normal patient

so if we now give a therapeutic dose of

a monocon anybody for example uh then do

is range dependent on anybody between um

it if few hand 00 uh mgam to perhaps

one or one and a half gr that is very

minor contribution to the overall amount

of IG thats in the body between 0 0

and 00 gram so by that you do not

change the overall IGG concentration in

the body and by that you do not affect

the FCI and recycling process so you

stay at this

point you would only change that process

if you give the massive amounts of um

immune globin G and thats sometimes

done by intervenous I I uh imunoglobulin

therapy or IVIG therapy where you give

massive amounts of I IVIG and that

instance you could imagine you increase

the serum concentration of IG by that

you start to saturate the FC recycling

process more molecules compete for the

same number of fcrn receptors and by

that you get a less efficient recycling

process in a shorter half

life the opposite could

occur uh or no another example for that

uh would be disease conditions where you

have a largely increased immune globulin

concentration one example for that is

multiple Myoma where sometimes you have

uh highly

increased uh

molecular species that interact with

fcrn and by that you have again more

competition so that if you now would

give a therapeutic protein that uses the

same recycling process uh you would end

up with a shorter half life due to this

competition for the fcn recycling

process so in summary for this section

the ne C receptor fcn is an efficient

mechanism of preventing monocon

antibodies and abum molecules from

undergoing Lal degradation leading to a

long resonance time and long terminal

halflife for these protein molecules all

IGG anybody derivatives with intact fcn

binding site on their constant FC domain

and all abum Fusion proteins underg go

FC mediated Recycling and follow

basically the same

processes

again here is a self

assessment question for this

section