we are fortunate to have dr ashley

dr greene is currently a chemist at the

national institute of standard and

technology and her research primarily

focuses on the standardization of

protein measurement and science

dr green received a bachelor of science

degree in biochemistry from spelman

college in 00 followed by a phd in

pharmacology from johns hopkins

dr green completed a postdoctoral

training at nist

please enjoy todays lecture

hello my name is dr ashley beasley green

and i am a staff scientist at the

national institute of standards and

technology and today i will talk to you

about biochemical mechanisms of drug

toxicity

heres a brief outline of the

presentation ill start with the adverse

drug reactions the impact

the economic and the prevalence of these

reactions some common mechanisms of

adverse drug reactions the type a the

intrinsic and type v the be the

idiosyncratic reactions

and also well discuss the risk

assessment of these drug reactions

the world health organization divine

defines a an adverse drug reaction as

being a response to a drug which is

unintended and which occurs at doses

normally used in man for prophylaxis

diagnosis or therapy of disease or

modification of physiological function

in the 0 national action plan for the

adverse drug event prevention which was

drafted by the us department of health

and human services its noted that

adverse drug events account for roughly

two million

inpatient hospital stays annually and

roughly

a little more than million office

outpatient office visits

and approximately million emergency

department visits

in addition to the high incidence of

adverse events

these events also pose a large economic

burden contributing to roughly

billion

of the

us health care costs

therefore it is extremely important to

understand basic drug mechanism of

action but also understand potential

adverse reactions that can occur during

drug therapy

in this first section i will highlight

several known adverse drug reactions and

examples of these reaction types

this is a very simplistic view

of drug metabolism here we have a drug

thats converted to nontoxic

metabolites and is then excreted through

urine

when bioactivation enzymes convert this

drug to reactive metabolites then we see

some of the adverse drug reactions

listed here are the two major reactions

we have the type a which is an intrinsic

reaction the type b which is the

idiosyncratic reactions in the type abe

reactions these reactions are dose

dependent therefore theyre predictable

and they also can occur at high

incidence

with low mortality however in the type b

case

these reactions are not dose dependent

therefore theyre unpredictable

and theyre dependent on the individual

genetic and also physiological

conditions so there is low incidence

of these types of reactions however

these types of reactions occur with high

mortality rates

so for um the first example ill

highlight a type a um adverse reaction

using the acetyl acetaminophen on drug

this is a wellknown and highly

characterized drug that is linked to

liver toxicity via the formation of

reactive metabolites

acetaminophen is a popular

overthecounter pain reliever and the

mode of action is the inhibition of the

prostaglandin h synthetase enzyme which

is used to convert arachidonic acid to

prostaglandin h

acetaminophen induced liver toxicity is

dose dependent as with most type a

adverse drug reactions

this drug is safe at therapeutic

concert

concentrations

however severe liver toxicity occurs

above the therapeutic range

in data collected from the us acute

liver failure study group

in january 0

it was defined it was identified that

acetaminophen was the leading cause of

acute liver

failure in most instances alf occurred

as a result of a suicide attempt via a

single dose over the therapeutic dose or

from extended use by patients seeking

pain relief these were the unintentional

overdoses

in 0 the us food and drug

administration

fda issued a final guidance to

manufacturers of the overthecounter

counter drug here is the guidance

and it can be located at this

web address

products

encouraging products to provide

alternative language to the liver

warning section of the products label

and here the warning states

liver warning this product contains

acetaminophen severe liver damage may

occur if you take either one with more

than 000 milligrams of acetaminophen

within hours

two with other drugs contained in

acetaminophen or

three with three or more alcoholic

beverages

drinks every day while using this

product

here is the

biochemical mechanism of acetaminophen

metabolism

we see the detoxification and

bioactivation pathways

approximately percent of the major

metabolites of acetaminophen

metabolism are in the inactive forms of

the glucoronide and the

sulfate conjugates

these conjugates are undergo renal

elimination um

and so then the this is the nonuh toxic

pathway of acetaminophen

however roughly ten percent of

acetaminophen is then converted through

the enzymatic activity of the p0

enzymes listed here to produce a

reactive metabolite as illustrated in

this very simplistic view of drug

metabolism

this this reactive metabolite is napqi

napqi is then further detoxified by

glutathione conjugation

this conjugate is then formed into a

cysteine or mercampturic acid adduct

these adducts are then eliminated

in urine

and doses higher than the therapeutic

dose

a known mechanism for drug induced liver

injury can occur via oxidative stress

in this case the reactive metabolite

which is the napqi

accumulates in glutathione is depleted

which prevents the

production of the

cysteine and mercampturic acid adducts

leading to urine excretion

so in the absence of sufficient

glutathione the napqi reactive

metabolite covalently binds to

liver proteins

this binding to the liver proteins

inhibits the function of these proteins

leading to further oxidative stress

increasing

oxidative stress and liver cell necrosis

leading to liver toxicity

although acetaminophen liver toxicity is

dose dependent there are several factors

that can enhance apap

susceptibility causing liver toxicity

alcohol consumption while taking

acetaminophen can increase the risk of

liver toxicity by increasing

bioactivation

of the acetaminophen molecule

when aloe when ethanol is present

it becomes an a competitive substrate

for the p0 enzyme illustrated here

this stabilizes the enzyme which then

induces the production of more of this

enzyme

when more of this enzyme is present it

increases the production of the

reactive metabolite the napqi

further leading to

further inducing the liver toxicity

effects of

acetaminophen so this is why the fda

illustrated in their guidance to

um

to reduce the consumption of

three or more alcoholic beverages in the

presence of acetaminophen because liver

toxicity is induced

under these conditions

although acetaminophen liver toxicity is

dose dependent

theres also

acetaminophen can also induce an immune

response

as you can see here there are several

interconnected mechanisms that can lead

to liver cell necrosis

liver toxicity following the

administration of acetaminophen at

certain levels

unlike type a

type b adverse drug reactions are not

dose dependent and the mechanism of

liver toxicity is not linked to the mode

of action

idiosyncratic means specific to an

individual

so these adverse reactions are

unpredictable

idiosyncratic drug reactions can affect

any organ the most common of these

organs being the liver skin and also

blood cells

therefore liver toxicity is

unpredictable it accounts for a large

percentage of drugs eliminated during

the preclinical testing

clinical trials and also the

postmarketing phase of the drug

discovery and development

process

because its unpredictable there is

limited mechanism mechanistic

understanding

there are several theories determined

via animal models for type b induced

liver toxicities

and i will discuss six of these eight

theyre highlighted here um

with the underlying

as previously discussed in the

acetaminophen example

in the reactive intermediate hypothesis

the drug is converted to the reactive

intermediate via bioactivation enzymes

and then can bind to

liver proteins eliciting a

drug induced liver injury

the reactive metabolite can also

increase oxidative stress leading to

mitochondrial dysfunction which can then

lead to liver dis liver dysfunction and

toxicity

also genetic variations of these

bioactivation enzymes can affect the

conversion of the drug to reactive

metabolites increase or either decrease

the production of these reactive

metabolites

an example of these three hypotheses is

the

iso niazid

this is the first line agent in the

treatment of active or latent

tuberculosis the mode of action is the

inhibition of mycolic acid formation

which is an extension essential

component of my

mycobacterial cell wall synthesis

an animal model was used to determine

the mechanism and approximately 0

percent of treated patients developed

elevated liver enzymes and bilirubin

the reactive metabolite in the in this

mechanism

or reactive inter intermediate in this

mechanism is the hydrazine

is then converted through the cytochrome

p0 enzymes to the to the toxic

metabolite which then increases

oxidative stress leading to liver

toxicity

acetyl transferase

nat illustrated here and here

acts at several points to reduce the

concentration of the reactive

intermediate hydrazine

however genetic variations of this

enzyme can decrease the activity leading

to an increase in the concentration of

the reactant intermediate hydrazine then

increasing the liver toxicity effects of

this drug

another hypothesis in the type b

adverse drug reactions is the hapten

hypothesis

in this hypothesis the drug or reactive

metabolite as seen here the drug or its

reactive form

covalently binds to a protein

forming the drug modified protein

the drug modified protein then acts as

an antigen and is processed and

presented on the

antigen presenting cells via the mhc

restrict in a mhc restricted manner

you can see that here

the antigen is subsequently presented to

t cells which can elicit immune

tolerance however in the danger

hypothesis the similar

cascade happens once the drug modified

protein is formed it is presented by the

hpc

however two signals are required in

order to activate the t cells

eliciting

an immune response from the drug

an example of a drug that forms drug

modified proteins and can elicit an

immune response is halothane

halothane is a volatile general

anesthetic administered via inhalation

it was introduced in the 90s and has

been associated with two types of

adverse liver events by different

pathways

the first pathway

this is type one here

presents mild liver toxicity halothane

undergoes reduction by the cytochrome

p0 enzyme illustrated here to produce

a radical

this radical

can form stable metabolites it can

inactivate the cyto cytochrome p0

enzymes or most importantly it can

initiate lipid peroxidation and it is

the lipid peroxidation that can elicit

the mild liver toxicity effects of this

particular

pathway the type pathway

or the severe liver toxicity pathway

in this pathway the mode of toxicity is

thought to be mediated by an immune

system

response via the form via the formation

of a drug modified protein so here in

this particular pathway halothane

undergoes oxidation by the cytochrome

p0 enzyme illustrated here

to produce a reactive metabolite that

can either form the

trifluoroacetic acid or can be

conjugated to liver proteins eliciting

an immune response as illustrated in the

previous slide

unlike halothane penicillin induced

adverse reactions or the anaphylaxis

reaction is classic is a classic example

of a hapten

penicillin is an is an antibiotic

and the betalactamarine

ring illustrated here

is the chemically reactive component of

this molecule

unlike many other drugs that require

metabolic activation in order to elicit

a response penicillin

directly binds to covalently binds to

proteins

generating the drug protein

conjugate

and it is this conjugate that is the

major antigen for the ige mediated

allergic reaction

there are several reactions several

tiers of reactions that can occur from

this drug protein conjugate the common

reactions such as diarrhea nausea rash

occurs roughly greater than one percent

of the population however

the true anaphylaxis response

only has an incidence of 00 percent

in order to test an individual for

sensitivity to penicillin the skin test

is administered a positive reaction

suggests that the individual should

avoid penicillin

this is

indicated by the presence of ig ige

antibodies to the penicillin compound

if needed desensitation desensitization

therapy can be

conducted further

however if a negative

result

is generated from the skin test

it indicates that the person is not

allergic to penicillin

or

we are unable to come with a actual

definitive

result so therefore a further analysis

is needed and one of those is the graded

dose challenge

in this challenge the individual

receives four to five doses of the

penicillin molecule

starting with a small dose and

increasing to the desired therapeutic

dose

if

the patient reaches the therapeutic dose

and there is no reaction then that drug

is administered and deemed that the

person does not have

a

allergic reaction to the penicillin

molecule

another

hypothesis for

a mechanism

leading to type b adverse reactions is

the inflammatory stress hypothesis

an idiosyncratic adverse drug reaction

is initiated in this type of hypothesis

when a drug therapy is coupled to an

acute inflammation episode

it is thought that the inflammatory

episode could lower the threshold for

toxicity therefore rendering a toxic

response at the safe and effective dose

examples of these inflammatory stresses

could be infection

a disturbance in the intestines or some

type of cell death

an example drug of this type of

hypothesis is trovan

tvx

this is a broad spectrum antibiotic and

it was strict restricted in

in 999 and withdrawn in 00 due to the

severe liver toxicity

it has been shown shown in mice models

that modest inflammatory stress renders

safe doses of tvx toxic

this is the mode of action of tvx

on the um bacterial dna

in the gram negative the

drug

interacts with the bacterial dna dna

gyrase

in the grampositive

organism the drug reacts with the

tesomerase

for

enzyme and so actually what happens is

the drug

binds to the

a component of the gyrase

enzyme therefore preventing the

separation and religation of the

doublestranded bacterial dna during

replication so this prevents the

replication of the bacterial dna during

the growth and production process

in this inflammatory drug interaction

mouth model which was developed by the

roth group and here you can

see the um

the reference for the data presented in

this slide

an inflammatory response is induced by

lipopolysaccharide

lps

in the mouse

and then the mouse is treated with tvx

following the lps exposure to determine

the effect of the drug on liver toxicity

in the presence of inflammation so this

is really to

prove that

tv

tvx administered in the presence of an

inflammatory

stress condition can elicit liver

toxicity

and here we see

alt actually is a biomarker for liver

health so thats how were measuring

liver health using a the alt a alt

marker

and the vehicle is just the sterile

saline

material

so in the saline system we dont see an

increase in liver in alt production or

liver injury however as we increase

as we administer the tvx in the presence

of the lps or the inflammatory stress

condition

we see an increase in alt

concentration leading to leading us to

suggest that at about 0 milligrams per

kilogram there is

liver

injury

with the administration of the tvx

molecule in

parallel with an lps induced

inflammatory response

and over time we can see here that

um roughly about after nine hours of

exposure to the lps

or the in or inducing the inflammatory

response we see an increase of liver in

injury or an increase in alt here at

about nine hours

so what does this really mean and how

can we really associate this increased

liver toxicity to

this inflammatory response in the

presence of this of this drug

so

the scientists here have looked at

the tumor necrosis factor alpha which is

tnf alpha tnf alpha is a mediator of

inflate inflammation and is involved as

a major factor in various liver injury

models

so its a good marker for

induced

its a good marker for inflammation

so what we see here is the vehicle and

also um

the vehicle with the tvx in the presence

of the lps so

tvx administered during an inflammatory

response

can increase the tnf alpha

so there definitely is

liver injury associated with this

inflammatory response

and we can see that here by looking at

alt so in the presence of tvx and lps we

see an increase of alt and an increase

of tnf tnf alpha meaning that the liver

injury is induced by the inflammatory

response associated with the

administration of

tvx and lps

however we see a reduction in tnf alpha

or inflammation and also alt or

liver injury in the presence of the

etanercept

drug etanercept is a specific inhibitor

of tnf alpha activity

so therefore were able to reduce the

inflammatory response so as we reduce

tnf alpha we also reduce the

inflammatory response in the presence of

the tvx

so

we can conclude that with this mouse

model when tvx is administered with an

inflammatory response which is induced

by the lps we see the

liver injury

further

confirming the hypo the inflammatory

stress hypothesis

in addition to the mild studies

the the team also did gene expression in

order to identify pathways that are up

regulated in the presence of the tvx and

lps system

the findings were the several pathways

associated with inflammation were

upregulated during treatment

with the tvx molecule

i want to highlight here that

in the analysis of drug candidates

during the drug discovery process gene

expression could be a potential

mechanism in order to identify drugs

that can elicit adverse reactions or

these type b reactions that are

somewhat unpredictable

in subjects especially with acute

inflammation

so with all of this information

about the type a type b

adverse drug reactions how do we develop

safe drugs

to address the high incidence and also

the economic impact risk assessment

strategies must be integrated earlier in

the drug discovery and development

process

extensive safety testing is conducted

during the preclinical phase

however to reduce attrition during this

phase and and also increase patient

safety during the clinical trials

and the postmarketing phases the risk

of drug candidates should be addressed

during the basic research and drug

discovery phase

so the earlier that we can identify

candidates that can elicit

adverse reactions

the safer we the patients will be

and we wont spend as much money because

this process is extremely expensive

here um in 0 the costs were estimated

to be roughly billion dollars for

this enti entire process so to have a

target go

all the way to post marketing and then

be restricted that is a huge economic

loss so we want to be able to

enhance patient safety but also reduce

the the risk of of of losing money by a

a drug inducing some of these

unpredictable adverse reactions

hazard identification and risk

assessment of reactive metabolites is

one way

that we can identify candidates that are

potential that pose potential hazards to

patients

the major difficulty

of identifying these drugs that can

elicit these type b reactions is the

complexity of the mechanisms involved

and also the gaps in our scientific

understanding of these drug induced type

b reactions

illustrated here is an adverse outcome

pathway you have the chemical insult the

macromolecular interaction

cellular tissue

and the organ response and then the

individual response so they are these

are different tiers of risk of drug

responses

this is a nice representation of the

various approaches that are currently

being

utilized to identify

drug targets that can elicit these

reactions

formation of reactive metabolite

approach

the metabolite formation combined with

the with the dose approach

and also combining the reactive

metabolite to

measuring the cellular response approach

so were looking at these first three

tiers of the adverse outcome pathway

the first

way

or

mode to assess the risk of drug

potential drug candidates is to remove

structural motifs

from the chemical library

that can elicit

or form these reactive metabolites

the elimination of these candidates

based on in silico assessment of

structure motifs reduces cost because no

synthesis of the compound is required

this approach minimizes risk of

developing a drug that can generate a

reactive metabolite therefore leading to

patient toxicity or patient injury

however

by eliminating these structural maltese

we reduce the chemical library of um for

drug candidates

for example

if the phenol and thiophene structural

motifs were eliminated from the chemical

library

many drugs that are safe and effective

would not be accessible to patients such

as abilify which is our antipsychotic

therapy or cymbalta

which is used to treat depression or

singulair which is used in the

maintenance treatment of asthma and also

to relieve symptoms of seasonal

allergies so we cant eliminate

all of these potential

toxic structural motifs but we also we

are we can eliminate some

another approach in identifying the

formation of these reactive metabolites

is a trapping approach

because of the instability of some of

these metabolites we need to stabilize

the metabolite in order to i to

characterize and detect them using these

trapping agents

and detecting the

trapping agent drug conjugate using

liquid chromatography mass spectrometry

approaches

this is an example of the trapping

approach used to identify

the primary intermediate of the

glycolysis pathway

which is the bispho

bisphosphoglycerate

or bpg for short

in

in the pathway glucose is converted to

gap

under the enzymatic activity of the gap

dh enzyme

gap is converted to bpg

this metabolite is extremely labile

it

simultaneously will convert or none

enzymatically will convert

to the pg or bpg

metabolites

therefore in order to

identify the bpg metabolite we must

find a way to stabilize this component

without it undergoing hydrolysis or

isomerization

one way one approach that um

[Music]

a group decided to

utilize the trapping approach in order

to capture the

bpg

molecule

hydroxylamine

reacts with bpg forming a stable

metabolite that is then able that that

were then able to identify using mass

spectrometry

this stable analog has a unique tandem

mass spectrometry profile

therefore allowing

the identification of the

therefore indirectly allowing the

identification of the bpg metabolite

here we see the bpg metabolite

without

any modification

and were unable to detect using mass

spectrometry

however when the bpg is

trapped or

conjugated to the hydroxylamine trapping

agent were able to identify the

modified

metabolite using mass spectrometry

and the removal of the phosphate group

um generates a nice peak at the 99 to

9

and then the 9

product precursor

product ion transition of 99 to 9 so

were able to detect the modified

molecule here

to assess the in vivo detection of the

analog or the conjugated bpg molecule

the group

looked at

cell culture

they modified the cell culture with the

trapping agent and then just added dmso

as our control

and then

extracted the

bpg

unmodified and modified virgins versions

and analyzed using mass spectrometry

here in this

bar graph we can see that the unmodified

version in the control

system compared to the modified versions

have similar

relative levels

however when we add

the naf

molecule which inhibits the activity of

inolase which leads to the accumulation

of bpg

we should expect to see an increase in

the bpg

metabolite

theres a slight increase over

um

in the naf system compared to the

control in the unmodified version

however in the modified version in the

naf system we see a huge increase a

significant increase in the modified

bpg metabolite so therefore modifying

the metabolite we get a

a more accurate view of the

concentration of the bp bpg metabolite

here we see the um mass spectrometry

spectra of the

modified versus the

unmodified in the presence of the naf

molecule and we we dont see

the peak in the

unmodified version of bpg but when

modified with the trapping agent we see

a peak

representing

the modified metabolite

they also looked at the concentration of

the modified metabolite with increasing

glucose and we can see here that as you

increase your glucose you increase the

amount of the modified bpg versus the

unmodified metabolite

so what does this all mean we can

actually

utilize trapping

agents in order to detect

highly unstable reactive metabolites

therefore allowing us to determine the

formation of these reactive metabolites

from drug candidates early on

there are other

methods that also can be used such as

the electrochemical approach and also

the time dependent inactivation approach

in order to identify these highly

unstable reactive metabolites

the information obtained from the

detection of these reactive metabolites

can be used to eliminate these drug

candidates or structural multis that can

form these reactive species

however the detection of reactant

species does not provide information

about the major mechanism of action

therefore more work is required to

assess the major and minor reactions

during drug metabolism so a drug so a

reactive metabolite may form but

through these approaches is unable to

determine if this is a major or minor

form of the mechanism

also

currently the assessment of reactive

metabolites using these approaches is

not compatible with the high throughput
flat platforms which are used during the
drug screening process therefore these
approaches cannot be used in these high
throughput settings during the early
stages of drug development
in addition to the formation of these
reactive metabolites we can also combine
the formation with the actual dose
incorporating the drug dose component to
the detection of these species and also
incorporating the formation of the drug
protein conjugates is an important is
important to identify toxic drug
candidates however due to the complexity
of the toxicity mechanism and in vivo
biological interactions that occur with
the drug it is difficult to establish
cut off values that would distinguish
safe versus unsafe drugs at early stages
in the development process
to address the complexity of the toxic
toxicity mechanism we can couple the
identification of these reactive
metabolites
with cellular responses

one mode to do that is using utilizing a

multifactorial approach

this can be used as a prediction tool in

order to distinguish between drugs that

have a high or low tendency to cause

these type b adverse reactions

in this approach we combine the covalent

binding burden

which is the quantitative estimate of

the ability of the drug to form a drug

protein conjugate

with in vitro panel

the in vitro panel consists of a series

of assays that are used to profile the

biological effects of drugs

this is an example of this

multifactorial tutorial approach

here we have a integrated in vitro

hazard matrix thats used in order to

detect

the

molecules that

elicit no hazard or have an extreme

extreme or severe

toxicity

in this particular experiment drugs

were screened in this in vitro panel and

also

the covalent binding burden was analyzed

in order to

generate a score that is then used to

plot this hazard matrix and out of the

were deemed severe or marked

idiosyncratic adr concern

so they had severe toxicity or um

teetering on the uh no hazard and

concern level

and nine it showed a no hazard result so

this particular approach can distinguish

between safe and unsafe drugs with high

sensitivity and specif specificity so

unlike the previous approaches where we

were just identifying the

reactive metabolite

or i

identifying the reactive metabolite

coupled to dose in this particular

approach were actually combining the

formation of this reactive metabolite

and also the effect of the drug on

various in vitro

components

the type b adverse reactions are complex

and unpredictable and in some cases they

can involve the immune system

therefore

to model these complex systems we need

models that show the interconnected

mechanisms that can occur within the

tissue or organs

so these existing

approaches

although here were looking at some of

the cellular responses we dont get to

capture

the inner

connection or interrelated mechanisms

associated with these tissues and higher

order

components such as organs

but in this micro physiological model

were able to capture some of these

complex biological interactions and the

effect that the drug has on these

interactions in order to identify

candidates early on in the drug

discovery process

that

can have toxicity to individuals

a free a few examples of these models

are listed here you can have a d

culture or liver culture model you can

have a cold culture

you can utilize bioreactors or media

flow

ill highlight one of these models in

order to

demonstrate how utilizing a more

sophisticated model to identify

drug toxicity at some of these lower or

basic research levels

would enhance the

determination of candidates that are

safe and those that are not safe to

individuals

in our previous example we looked at tvx

tvx is a known antibiotic and here we

can we see the

mode of action that was discussed

earlier

the motivation for liver toxicity was

identified

utilizing an animal animal model

where they utilize lps in the presence

of tvx and showed that we can

elicit a liver

toxicity in the presence of the in an

inflammatory stress condition

however

what if we can use an in vitro model

in order to determine

inflammationmediated drug toxicities

in this particular approach

this group

developed a

d liver micro tissue

the kelm group

and the nice and its called the d

human liver

micro tissue or the d insight human

liver micro tissue the nice thing about

this approach is that its in a 9 well

format so it is conducive to the high

throughput screening process that occurs

in the drug screening or basic research

process during the drug discovery

this is a d

liver micro tissue that has been

converted to the high throughput format

the

tissue is stable and functional over

five weeks in culture

as illustrated in these graphs we see

the atp

quantification of atp and the albumin

secretion so were able to look at cell

vitility and also functionality over

five weeks so theyre confident that

this particular molecule can show

longterm

effects of drug treatment

so here we have data that

um

utilizes this d

human liver

model in order to

demonstrate the effects of tvx in the

presence of inflammation

on liver injury

and we can see here that

as we increase

or as we expose

the micro tissue to lps inducing

um

inflammatory response

we can actually

and and also administer the tvx

molecule we actually increase

or decrease the threshold

of the drug in the presence of the

inflammation episode

inducing the liver

toxicity

so this is a nice model that provides

the ability to identify drugs that

elicit these

adverse reactions early during the drug

discovery phase so with this particular

model were able to look at some of the

human

biological mechanisms

that can contribute to drug toxicity

instead of conferring an animal model to

what could happen happen

in a human

subject in addition to d models we can

also utilize computational models

in order to provide a costeffective and

safe way in order to screen compounds

for toxicity by simulating complex

processes during drug drug metabolism so

in addition to making these molecules

and ensuring that we have the correct

and optimal environments for growth and

then

ensuring that we can actually

see a response

after drug administration we can do some

computational models and the nice thing

about the computational models is that

we can actually generate some of these

mechanisms that we cant generate in

vivo

in order to really capture what occurs

after a drug is administered and we can

do this early on in the drug development

process

so there are several bio

biochemical mechanism

mechanisms

that occur through drug toxicity

and ive highlighted several

um

that

can lead to drug toxicity and ive also

talked about some emerging technologies

that can that we can utilize

in order to minimize the risk of drug

toxicity so instead of waiting through

the preclinical or clinical

or

at the worst case waiting to

a drug is

removed from the market during the

postmarketing

phase we can utilize some strategies

such as

the

d

micro tissue model or some of these

computational models in order to

investigate drug targets during the

basic research phase to determine which

of these targets have the potential to

elicit some of these adverse drug

reactions

therefore

enhancing the safety of patients in the

clinical trials and also patients

taking the therapies

the key theme throughout this

presentation

is the need to identify drug toxicity

early in the developmental process in

order to reduce the risk of pain to

patients

during as i mentioned on the clinical

trials and also the postmarketing phase

so there are a number of mechanisms that

can contribute to drug toxicity

and in one way to

reduce the risk is to start early in the

development process utilizing gene

expression or d model

micro tissues or computational modeling

in order to identify

potential targets that can elicit

adverse reactions

so i would like to

leave you with this thought

i hope that the information that was

presented here in these slides will give

you more information about some of the

mechanisms involved in drug test

toxicity but also

start you to think about

some potential strategies that can be

can be implemented in order to reduce

the risk to patients but also

maintain the

effectiveness of drug therapies so the

idea is to

enhance the drug therapy but also reduce

the risk to patients and we can do that

by

looking at some of these models early on

in basic research that can model

that can more effectively model the

human

systems

in

allowing for a more detailed and

indepth ideal or

basis for drug toxicity in humans so i

want you to kind of think about what are

some

current

approaches that can be applied and what

are some new approaches that can be

developed in order to reduce the cost of

drug discovery and enhance the risk or

reduce the risk to patients

in these drug therapies

thank you for your attention and thank

you for

taking time to look at some of the

information i provided here in the

slides

again my name is dr ashley beasleygreen

and if you have any questions or

comments regarding the material that i

provided in my presentation please

direct all of your questions or concerns

to the program coordinator again thank

you and start the conversation about how

we reduce risk to patients by utilizing

some of these scientific approaches to

identify drugs that can elicit adverse

reactions early on during basic research

and analysis thank you