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# Appendix

## Abbreviations

BAC: Bacterial Artificial Chromosome
BF: Blocking Factor
CF: Competence Factor
(h)ES cell: (human) Embryonic Stem cell
EpiSC: Epiblast derived Stem Cell
FISH: Fluorescent *In Situ* Hybridization
ICM: Inner Cell Mass
(h)iPS cell: (human) induced Pluripotent Stem cell
iXCI: imprinted X Chromosome Inactivation
Mb: Mega base
MSCI: Meiotic Sex Chromosome Inactivation
MYA: Million Years Ago
OMIM: Online Mendelian Inheritance in Man database
PAR: Pseudoautosomal Region
PGCs: Primordial Germ Cells
rXCI: random X Chromosome Inactivation
TBP: TATA Binding Protein
Xa: active X chromosome
XAR: X Added Region
Xce: X controlling element
XCI: X Chromosome Inactivation
XCR: X Conserved Region
Xi: inactive X chromosome
Xic: X inactivation center
XicHR: X inactivation center Homologous Region
*Xist*: X inactive specific transcript
Xm: maternally derived X chromosome
Xp: paternally derived X chromosome, or short art of the human X chromosome
*Xpr*: X pairing region
Xq: long arm of the human X chromosome
YAC: Yeast Artificial Chromosome

## Summary

The evolution of placental mammals has resulted in a genetic mechanism of sex determination with X and Y sex chromosomes, where females of most species have two X chromosomes and the males have a single X chromosome and a small Y chromosome. These sex chromosomes originated from a non-sex-specific pair of autosomes. In males the deterioration of the Y chromosome resulted in a loss of genes, compared to the X chromosome. To balance this loss, the single X chromosome in males became transcriptionally up-regulated, resulting in a dosage compensation mechanism between genes located on the sex chromosomes and genes on autosomes. In females, this up-regulation of X-linked genes resulted in a subsequent dosage problem, as two copies of X chromosomes are present. Therefore, in females, an additional dosage compensation mechanism was required, which results in the transcriptional silencing of a single X chromosome in females. This silencing of an X chromosome in females, leaving one active X chromosome per diploid genome, is called X chromosome inactivation (XCI), and is the central topic in this thesis work.

XCI occurs during early female embryonic development, and results in transcriptional silencing of one X chromosome in females, thereby equalizing the dosage of X-linked genes between both sexes and between the sex chromosomes and autosomes. This is needed for proper biochemical and physiological functioning of cells in the body, as gene products derived from the X chromosome need to interact with gene products from autosomal genes. Aberrations of the crucial XCI process are believed to be lethal, as no healthy females are observed having more than one active X chromosome, and females in which parts of both X chromosomes are fully active suffer from severe phenotypes. The XCI process itself is random regarding the choice of the X chromosome that will be inactivated, resulting in silencing of either the X chromosome derived from the father or the X chromosome derived from the mother, in the cells forming the embryo. Therefore, growing and adult females consist of a mosaic of two different cell populations, which can have profound impacts on health and disease manifestations in females, as described in the Introduction in Chapter 1. Many genes located on the X chromosome can cause diseases when mutated. In general, females suffer less from X-chromosomal diseases, due to the presence of the mosaic, in which some cells will express the mutant gene, whereas others will express the non-mutated backup copy from the healthy X chromosome. Such a backup mechanism is not possible in males carrying a single X chromosome, who therefore always show expression of an X-linked mutation. Besides this advantage for females, of having two X chromosomes, there is also a disadvantage. The XCI process seems to be difficult to establish properly in all female cells, which might explain higher female lethality during peri-implantation development. Furthermore, the presence of mosaicism can sometimes cause a disease, when the choice of inactivation is not random between the X chromosomes present. Therefore, insight in the mechanisms resulting in epigenetic silencing of a single X chromosome in females is needed, and XCI is an important subject to study.

Following the initial discovery of the XCI process in 1961 by Mary Lyon, many investigations have tried to unravel the mechanisms leading to the shut-down of one X chromosome in females. Most of these studies have been performed in mice, by making use of either genetic mouse models or embryonic stem (ES) cells. ES cells are pluripotent cells derived from early embryos, and can be used to study several aspects of the XCI process in a culture dish, as undifferentiated female ES cells have two active X chromosomes, and upon differentiation to more specialized cells these cells engage in XCI, similar to what happens in early embryonic development. By making use of these models, studies have shown that a small region of the X chromosome, the X inactivation center (Xic), is crucial for XCI to occur, as this process is only initiated in cells having two copies of this regulatory region on two distinct X chromosomes. The Xic harbors several conserved genes, of which the *X inactive transcript* (*Xist*) is crucial for XCI to occur. *Xist* is the only gene which is specifically expressed from the inactive X chromosome, and transcription of this gene results in a non-coding RNA, which spreads along the X chromosome and induces silencing. Another non-coding gene, *Tsix*, has been found in the Xic, and this gene is transcribed in the opposite direction to *Xist* and functions as a negative regulator of *Xist*.

During female embryonic development, or upon ES cell differentiation, *Xist* is specifically up-regulated on a single X chromosome, thereby starting the XCI process. Even 20 years after the discovery of *Xist*, a longstanding question has remained how this gene is specifically up-regulated on a single X chromosome in cells having more than one X chromosome. Several models have tried to explain this female specific initiation of XCI, and in the past, we have proposed that sex-specific initiation of XCI is regulated by a stochastic process. In this model, autosomally-encoded XCI-inhibitors prevent XCI in undifferentiated cells or cells in early embryos, by directly inhibiting *Xist* or stimulating *Tsix*. These XCI-inhibitors are encoded by genes located on autosomes, in both sexes, so that an identical level of XCI repression will be present. In contrast, X-encoded activators of XCI will stimulate the XCI process. These activators are encoded by X-linked genes, which implies that in females a two-fold higher dosage of XCI-activators will be present compared to males. These activators are most likely developmentally regulated, with low or absent expression in undifferentiated cells. Therefore, in undifferentiated cells, XCI will be absent, and will only be initiated during differentiation, as XCI activators will become up-regulated. This up-regulation will most likely occur in both sexes, but only in females the level of activation will be high enough to reach a threshold which is set by the combined action of the XCI-inhibitors. In this model, XCI-activators work in *trans*, meaning that they can activate XCI on all X chromosomes in a cell nucleus, independent from which X chromosome they are derived, resulting in a stochastic choice which *Xist* allele will become up-regulated. Once up-regulation has occurred, silencing of the XCI-activator gene in *cis*, thus on the same X chromosome where *Xist* will spread, will also silence the XCI-activator gene. Hence, the level of XCI-activator will drop, to a level which is now similar to that of a male cell harboring a single X chromosome. This simple mechanism ensures that XCI initiation on the other X chromosome will be prevented. *Tsix* is also silenced in *cis*, so that XCI can be maintained on the X chromosome which has started inactivation despite the lower level of the XCI-activators. Therefore, in this model, initiation of XCI is regulated by a sex-specific dosage difference in XCI-activators.

Although this model could principally explain all features of the XCI initiation mechanism, the identity of the XCI-activator genes remained illusive. We therefore set out to identify genes encoding such activators. By making use of a Bacterial Artificial Chromosome (BAC) transgenesis screen in ES cells, described in Chapter 2, we identified X-encoded RNF12 as the first known XCI activator. When *Rnf12* was over-expressed in male ES cells, this resulted in XCI initiation on the single X chromosome, and over-expression in female ES cells resulted in XCI on both X chromosomes in a significant portion of cells. During differentiation of ES cells, endogenous *Rnf12* becomes up-regulated, and a two-fold higher dose of RNF12 has been found in female compared to male ES cells prior to and during XCI initiation. After XCI has occurred, expression levels are equal between male and female cells. This two-fold higher dosage of RNF12 explains female specific initiation of XCI, as only in female cells a threshold will be reached upon differentiation which is needed to overcome repression of XCI by XCI-inhibitors, resulting in *Xist* accumulation. These XCI-inhibitors are mainly pluripotency associated factors, which either repress *Xist* directly, or indirectly, via stimulation of *Tsix* expression, or they might even work via repression of XCI-activators. In line with this, over-expression of *Rnf12* even leads to initiation of XCI in undifferentiated cells, indicating that absence of XCI-activator activity is important in preventing XCI in undifferentiated cells. More evidence for an important role of RNF12 in the initiation of XCI was obtained when one of the two copies of *Rnf12* was removed from female ES cells, as this resulted in delayed XCI initiation in these cells, favoring inactivation of the X chromosome harboring the *Rnf12* deletion. To generate this and other genetic modifications of ES cells described throughout this thesis work, we developed a new BAC targeting strategy described in Chapter 3, which makes use of polymorphic ES cells. Chapter 4 discusses the identification of RNF12 as an XCI-activator, and describes this discovery in more detail in the context of the stochastic model of XCI initiation. We next asked the question whether RNF12 is essential for XCI to occur, by generation and analysis of *Rnf12* knockout ES cells, described in Chapter 5. These cells were found to be devoid of XCI, providing evidence that XCI is not occurring in the absence of this crucial activator. Additional genetic experiments performed indicated that the XCI-activating function of RNF12 works mainly on *Xist*, as *Xist* transgenes were higher expressed when *Rnf12* was over-expressed, whereas the expression of *Tsix* transgenes was not affected. As RNF12 is an E3 ubiquitin ligase, it seems likely that such *Xist* activation should involve an indirect mechanism, in which RNF12 would target a repressor of *Xist* for proteasomal degradation. Indeed, studies aiming to identify the interaction partners of RNF12, described in Chapter 6, indicated that RNF12 targets the pluripotency associated transcription factor REX1 for degradation. REX1 was found to bind the *Xist* promoter and distal region, thereby repressing *Xist* expression in undifferentiated cells. Upon differentiation, *Rnf12* will become up-regulated, leading to a dose-dependent catalysis of the breakdown of REX1, which will result in loss of repression of *Xist*, and hence will lead to initiation of XCI. The *Rnf12* gene is located in the near vicinity of *Xist*, which ensures rapid silencing of *Rnf12* transcription in *cis* shortly after initiation of XCI. Chapter 7 addresses the question whether other genes located between *Xist* and *Rnf12* are also functional in the regulation of the XCI process. We found that *Jpx*, *Ftx* and the *Xpr* region have a *cis* regulatory role, in which these regions likely create an active environment, which is needed to enable activation of *Xist* by the *trans* action of

RNF12. We propose to divide the Xic in a *cis*-Xic, composed of all genes and elements involved in the regulation of *Xist* and *Tsix* expression in *cis*, and a *trans*-Xic, which is required for *trans* regulation of the *cis*-Xic, and hence for counting the number of X chromosomes present. We also provide evidence which suggest that direct interaction between the two X chromosomes in a female nucleus, referred to as X-pairing, is not functionally required for XCI to occur. Rather, more evidence was obtained supporting an indispensible role for the *trans* action of RNF12, even for the maintenance of XCI initiation.

We next proceeded to test the role of RNF12 *in vivo*, by generating an *Rnf12* knockout mouse model, described in Chapter 8. As expected from the observations showing loss of XCI in *Rnf12* homozygous knockout ES cells, homozygous *Rnf12* knockout females are not born, suggesting that RNF12 has an important role in XCI initiation during *in vivo* development. Females heterozygous for the *Rnf12* mutation also have an XCI phenotype, with transcriptional activity from two X chromosomes in some cells from adult tissues representing loss of XCI. This surprising and remarkable phenotype might make it necessary to change the dogma that living with two active X chromosomes is not possible. This awaits detailed investigation, but promises to have important implications for the understanding and future therapies of X-linked diseases in humans. Finally, in Chapter 9, we proceeded to translate the newly obtained knowledge on the regulation of XCI initiation from mouse to human. We studied XCI in female human induced pluripotent stem cells, and provide evidence that the X chromosome that is inactivated in a founder human fibroblast becomes reactivated upon somatic reprogramming. This might allow future generation of novel model systems to study XCI in humans. The General Discussion, Chapter 10, aims to integrate our current views on the initiation of XCI with previously published observations, and provides an outlook for future investigations.

In conclusion, the work described in this thesis has allowed us to obtain novel insights in the mechanisms controlling the initiation of XCI, including the role of RNF12, and provides a framework for future studies investigating the possibility to live with two active X chromosomes.

## Samenvatting

De evolutie van zoogdieren heeft geresulteerd in een genetisch mechanisme van geslachtsdeterminatie waarbij vrouwen van de meeste soorten twee X geslachtschromosomen hebben, in tegenstelling tot mannen met een enkel X chromosoom en daarnaast een Y geslachtschromosoom. De X en Y geslachtschromosomen zijn ontstaan uit een niet-geslachtsgebonden chromosomenpaar. Het snelle verlies van genen van het Y chromosoom, in tegenstelling tot een geleidelijke toename van het aantal genen op het X chromosoom, heeft geresulteerd in een situatie waarbij het X chromosoom verreweg de meeste genen bevat. Het Y-chromosomale verlies van genen werd gecompenseerd door een verhoging van de gen-transcriptie van het enkele X chromosoom in mannen, zodat een vergelijkbare dosis van geslachtsgebonden en niet-geslachtsgebonden genen behouden werd. Aangezien vrouwen twee X chromosomen hebben, zou een dergelijke verhoogde transcriptie van X-chromosomale genen tot een nieuw gendosis-probleem in vrouwen leiden. Dit werd voorkomen door een mechanisme, waarbij één van beide X chromosomen van de vrouw wordt uitgeschakeld. Dit proces, genaamd X-chromosoom-inactivatie (XCI), resulteert in niet meer dan één actief X chromosoom per vrouwelijk diploid genoom, en is het centrale onderwerp van dit proefschrift.

XCI vindt plaatst tijdens de vroege embryonale ontwikkeling van vrouwen, en resulteert in het uitschakelen van één van beide X chromosomen, waardoor de juiste dosis van X-gebonden genen tussen de geslachten, en tussen de geslachts- en de niet-geslachtsgebonden chromosomen behouden blijft. Dit is noodzakelijk om belangrijke processen in cellen goed te kunnen laten verlopen, aangezien veel genproducten van het X chromosoom in de juiste verhouding moeten kunnen samenwerken met genproducten van andere chromosomen. Afwijkingen in het cruciale XCI proces zijn dan ook embryonaal lethaal. Er zijn geen gezonde vrouwen waarbij volledige activiteit van beide X chromosomen werd vastgesteld, en zelfs de dubbele activiteit van kleine delen van het X chromosoom kan leiden tot aanzienlijke ziekteprocessen. Het XCI proces zelf kent een aspect van toeval, waarbij in cellen van het vrouwelijke embryo het X chromosoom verkregen van moeder of het X chromosoom verkregen van vader wordt uitgeschakeld. Door dit willekeurige proces zijn vrouwen een mozaïek van twee verschillende celpopulaties, hetgeen een aanzienlijk effect kan hebben op de manifestatie van ziekten, zoals beschreven in de Inleiding in Hoofdstuk 1. Vele genen gelokaliseerd op het X chromosoom kunnen ziekten veroorzaken indien zij afwijkend zijn, maar over het algemeen zijn ziekteverschijnselen bij vrouwen dankzij dit mozaïek milder vergeleken met mannen, aangezien veel cellen in vrouwen het intacte gen tot expressie zullen brengen. In mannen is een dergelijk back-up mechanisme niet mogelijk, en daarom zullen afwijkingen op het enkele X chromosoom altijd tot uitdrukking komen. Afgezien van deze voordelen voor vrouwen, zijn er ook nadelen verbonden aan het bezit van twee X chromosomen. Er zijn aanwijzingen dat het moeilijk is om het XCI proces goed te laten verlopen in alle vrouwelijke cellen tijdens de embryonale ontwikkeling, hetgeen de hogere sterfte van vrouwelijke embryo's tijdens de vroege embryonale ontwikkeling voorafgaand aan en rondom de implantatie fase zou kunnen verklaren. Tevens kan de aanwezigheid van een mozaïek soms ook problemen veroorzaken, in het bijzonder als de keus tussen het inactiveren van één van de X chromosomen niet willekeurig is. Daardoor is het van belang

om meer over dit belangrijke proces, dat kan worden gekenmerkt als een epigenetisch proces, te weten te komen.

Sinds de ontdekking van het XCI proces door Mary Lyon in 1961, zijn vele studies gewijd aan het ontrafelen van de mechanismen die er toe leiden dat in vrouwen één X chromosoom wordt uitgeschakeld. Het merendeel van deze studies heeft gebruik gemaakt van muismodellen of muis embryonale stamcellen (ES cellen). ES cellen zijn pluripotente cellen, nog niet gedifferentieerd, verkregen uit embryo's, die gebruikt kunnen worden om het XCI proces in een kweekschaal te bestuderen. Ongedifferentieerde vrouwelijke ES cellen hebben twee actieve X chromosomen, maar ondergaan het XCI proces als deze cellen naar andere, meer gespecialiseerde celtypen worden gedifferentieerd, waarbij deze cellen een eerste differentiatiestap tijdens de vroege embryonale ontwikkeling simuleren. Door gebruik te maken van deze modellen hebben studies laten zien dat een klein gedeelte van het X chromosoom, het zogenaamde X inactivatie centrum (Xic), vereist is om XCI plaats te laten vinden. Meerdere, in verschillende soorten geconserveerde, genen zijn gelokaliseerd in dit Xic, en het meest belangrijke is het *X inactieve transcript* (*Xist*) gen *Xist* is het enige gen dat specifiek actief is op het inactieve X chromosoom, en transcriptie van dit gen resulteert in een niet-coderend RNA, hetgeen over het X chromosoom kan spreiden en daardoor het X chromosoom kan uitschakelen. Een ander gen, *Tsix*, is tevens gelokaliseerd in de buurt van *Xist*. *Tsix* wordt in de tegenovergestelde richting afgeschreven in vergelijking met *Xist*, en is een negatieve regulator van het *Xist* gen.

Tijdens de vroege embryonale ontwikkeling van vrouwen of tijdens ES cel-differentiatie wordt het XCI proces gestart met de specifieke verhoging van transcriptie van het *Xist* gen. Ondanks dat het reeds 20 jaar geleden is dat *Xist* ontdekt werd, blijft een belangrijke vraag hoe het komt dat dit gen alleen wordt geactiveerd als meer dan één X chromosoom aanwezig is in de celkern. Verschillende modellen hebben geprobeerd om dit te verklaren, en wij hebben een stochastisch model voorgesteld. In dit model wordt XCI in ongedifferentieerde ES cellen of vroege embryo's voorkomen door de werking van XCI-remmers, die gecodeerd worden door niet-geslachtsgebonden chromosomen. Deze remmen *Xist* direct, of stimuleren de negatieve regulator *Tsix*. Aangezien in dit model de XCI-remmers afkomstig zijn van genen op niet-geslachtsgebonden chromosomen, zal de mate van repressie in vrouwelijke en mannelijke cellen gelijk zijn. In tegenstelling tot deze XCI-remmers, leiden XCI-activatoren tot activatie van het XCI proces. Indien deze XCI-activatoren gecodeerd worden door genen gelokaliseerd op het X chromosoom, zal in ongedifferentieerde vrouwelijke cellen met nog twee actieve X chromosomen een tweevoudige dosis van activatoren aanwezig zijn vergeleken met mannelijke cellen die maar één X chromosoom hebben. Naar verwachting zijn XCI-activatoren ontwikkelingsbiologisch gereguleerd, zodat ze tijdens ongedifferentieerde celstadia laag, of zelfs geheel niet, tot expressie komen. Hierdoor zal het proces van XCI in ongedifferentieerde cellen niet op gang komen. Echter tijdens differentiatie en verdere ontwikkeling van de cellen zal de expressie van deze XCI-activator genen toenemen, in beide geslachten. De twee actieve X chromosomen in vrouwelijke cellen zorgen voor een hoge dosis XCI-activatoren, voldoende om de remming van het XCI proces door de XCI-remmers te overkomen. De XCI-activatoren werken in *trans*, hetgeen betekend dat ze zowel XCI op het X chromosoom van waar zij geproduceerd worden als ook op alle andere X chromosomen in de celkern kunnen activeren. Dit heeft tot gevolg dat het een

willekeurige keuze zal zijn, welke kopie van *Xist* geactiveerd wordt. Eenmaal geactiveerd, zal *Xist* RNA over het X chromosoom spreiden, in *cis*, en X chromosomale genen op datzelfde X chromosoom uitschakelen. Hierdoor worden ook vrij snel de XCI-activator genen uitgeschakeld, hetgeen er voor zal zorgen dat de concentratie van XCI-activatoren in de celkern weer zal afnemen, zodat XCI niet plaats kan vinden op het tweede X chromosoom in dezelfde celkern. Aangezien de negatieve regulator *Tsix* ook wordt uitgeschakeld, zal de lagere dosis XCI-activator, die nu vergelijkbaar is met de dosis in mannelijke cellen, voldoende zijn om initiatie van XCI te behouden. Samengevat, in dit model wordt initiatie van het XCI proces dus gereguleerd door een geslachtsspecifiek verschil in de dosis van XCI-activatoren.

Hoewel dit model in principe alle eigenschappen van het XCI proces zou kunnen beschrijven, was de identiteit van de XCI-activator nog onbekend. We hebben daarom dit onderzoek gestart met een zoek-strategie om deze XCI-activatoren te identificeren, waarbij we gebruik maakten van bacteriële artificiële chromosomen (BACs) die we tot hoge expressie brachten in ES cellen. Door deze strategie, die beschreven staat in Hoofdstuk 2, ontdekten wij dat het door het X-chromosoom gecodeerde RNF12 eiwit de functie van XCI-activator kan uitoefenen. Wanneer het *Rnf12* gen tot hoge expressie werd gebracht in mannelijke ES cellen, resulteerde dit in XCI initiatie van het enkele X chromosoom in deze mannelijke cellen, en hoge expressie in vrouwelijke ES cellen resulteerde in XCI van beide X chromosomen in een hoog percentage van de cellen. Tijdens differentiatie van ES cellen komt het normaal aanwezige X-gebonden *Rnf12* gen ook hoger tot expressie, en een tweevoudige dosis van RNF12 werd gevonden in vrouwelijke cellen, vergeleken met mannelijke cellen, voor en tijdens XCI initiatie. Nadat de initiatie van het XCI proces is afgerond, is de hoeveelheid RNF12 gelijk tussen cellen van beide geslachten. Met dit dosis-afhankelijke mechanisme kan worden verklaard dat initiatie van XCI plaatsvindt in vrouwelijke cellen. De XCI-remmers zijn met name betrokken bij het in stand houden van de pluripotente staat van ongedifferentieerde cellen, en remmen *Xist* direct, of indirect via stimulatie van *Tsix* expressie. Tevens zouden zij kunnen werken via remming van de XCI-activatoren. Dit laatste wordt ondersteund door de vinding dat hoge expressie van RNF12 reeds tot activatie van XCI leidt in ongedifferentieerde cellen, hetgeen erop wijst dat remming van XCI-activatoren een belangrijk mechanisme zou kunnen zijn om XCI in ongedifferentieerde cellen te voorkomen. Meer bewijs voor een belangrijke rol van RNF12 bij de initiatie van XCI werd verkregen door het genetisch verwijderen van één van de twee X-gebonden *Rnf12* genen in vrouwelijke ES cellen. Dit resulteerde in vertraagde initiatie van XCI in deze cellen, die bij voorkeur het X chromosoom waarop het gemuteerde *Rnf12* gen was gelokaliseerd uitzetten. Om deze en andere genetische modificaties van ES cellen te bewerkstelligen, ontwikkelden wij een nieuwe BAC targeting strategie, die beschreven staat in Hoofdstuk 3 van dit proefschrift, en die gebruik maakt van polymorfe ES cellen verkregen door kruisingen van verschillende muizenstammen. In Hoofdstuk 4 bespreken we meer uitvoerig de bevindingen verkregen uit de *Rnf12* proeven, en zetten we deze uiteen in de context van het stochastische model van XCI. In het vervolg vroegen wij ons af of RNF12 een essentiële rol heeft in het XCI proces. Om dit te beantwoorden genereerden wij *Rnf12* knockout ES cellen, zoals beschreven in Hoofdstuk 5. In deze cellen bleek XCI niet op te treden tijdens differentiatie, hetgeen bevestigd dat RNF12 een cruciale rol bij het tot stand brengen van dit XCI proces speelt. Andere experimenten lieten zien dat de XCI-

activerende functie van RNF12 voornamelijk via *Xist* activatie werkt, aangezien *Xist* transgenen hoger tot expressie kwamen wanneer *Rnf12* tot hoge expressie werd gebracht, terwijl expressie van *Tsix* transgenen niet werd beïnvloed. RNF12 is een E3 ubiquitine ligase, een enzym dat betrokken is bij proteasomale eiwit-afbraak, en het is daarom aannemelijk dat deze *Xist* activatie verloopt via een indirect mechanisme, waarbij RNF12 een remmer van *Xist* zou markeren voor afbraak. Inderdaad lieten studies beschreven in Hoofdstuk 6 zien dat RNF12 de pluripotentie-geassocieerde transcriptiefactor REX1 target voor deze vorm van afbraak. We vonden dat REX1 bindt aan de *Xist* promotor, waardoor het de expressie van *Xist* remt in ongedifferentieerde cellen. Tijdens differentiatie komt RNF12 hoger tot expressie, hetgeen zal leiden tot een dosis-afhankelijke afbraak van REX1, waardoor de rem op *Xist* expressie verdwijnt en het XCI proces op gang zal komen. Op het X chromosoom is *Rnf12* dicht bij *Xist* gelokaliseerd. Dit zorgt ervoor dat na XCI initiatie *Rnf12* spoedig wordt uitgeschakeld in *cis*. In Hoofdstuk 7 behandelen wij de vraag of ook andere genen in de buurt van *Xist* en *Rnf12* betrokken zijn bij het XCI proces. Hier vonden wij dat *Jpx*, *Ftx* en de *Xpr* regio een rol spelen in de *Xist* regulatie in *cis*, hetgeen nodig zal zijn om RNF12 in staat te stellen om *Xist* in *trans* te kunnen activeren. Daarom stellen wij een nieuwe indeling van het Xic voor, waarbij we spreken van een *cis*-Xic, een regio die alle genen en elementen bevat die noodzakelijk zijn voor de *cis* regulatie van *Xist* en *Tsix*, en een *trans*-Xic, die nodig is voor de *trans* regulatie van de *cis*-Xic, met andere woorden voor het tellen van de hoeveelheid X chromosomen die aanwezig zijn. Verder vonden wij in experimenten beschreven in hetzelfde Hoofdstuk dat directe interactie tussen de beide X chromosomen, aangeduid met *X-pairing*, niet noodzakelijk is voor normale regulatie van XCI. In tegenstelling daarvan brachten deze experimenten verder inzicht in de belangrijke rol van RNF12 ook tijdens het in stand houden van de XCI. Om vast te stellen of RNF12 inderdaad een belangrijke rol *in vivo* speelt hebben wij een *Rnf12* deficiënt muismodel ontwikkeld, hetgeen beschreven staat in Hoofdstuk 8. Zoals reeds verwacht aan de hand van de *Rnf12* knockout ES cellen die geen XCI meer initiëren, bleken vrouwelijke *Rnf12* knockout muizen niet levensvatbaar, hetgeen suggereert dat RNF12 ook een belangrijke rol speelt tijdens de embryonale ontwikkeling *in vivo*. Heterozygote $Rnf12^{+/-}$ vrouwtjes hebben ook een XCI fenotype, waarbij in volwassen muizen cellen aanwezig zijn die twee actieve X chromosomen hebben. Deze verrassende vinding dient verder te worden onderzocht, en zou belangrijke nieuwe inzichten kunnen verschaffen over onze kennis en mogelijk nieuwe behandelingen van X-chromosomale ziekten. Tevens kan aan de hand van dit muismodel wellicht het dogma worden bijgesteld, waarbij ervan wordt uitgegaan dat de aanwezigheid van twee actieve X chromosomen niet levensvatbaar is. Tenslotte, in Hoofdstuk 9 proberen we onze nieuwe inzichten in de XCI regulatie in muizen te vertalen naar de mens, waarbij we XCI hebben bestudeerd in vrouwelijke humane geïnduceerde pluripotente stamcellen. Hier vonden wij dat het geïnactiveerde X chromosoom in humane fibroblasten tijdens het reprogrammeren gereactiveerd wordt. Dit kan mogelijk helpen om toekomstige modelsystemen te genereren om humane XCI te bestuderen. De Algemene Discussie in Hoofdstuk 10 vat de gevonden data samen, integreert deze met eerder gepubliceerde studies en biedt een vooruitzicht op toekomstige studies. Concluderend heeft het werk beschreven in dit proefschrift bijgedragen aan nieuwe inzichten in de regulatie van XCI en de rol van RNF12 hierin, en biedt het een basis voor toekomstige studies die zullen onderzoeken in hoeverre het mogelijk is om met twee actieve X chromosomen te leven.

## *Curriculum Vitae*

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| 2007-2008 | Department of Reproduction and Development<br>Master thesis "*Searching for an X-linked activator of X chromosome inactivation*", supervisor Prof.dr. Joost Gribnau |
| 2006-2007 | Department of Experimental Pathology<br>Internship, "*Characterization of tumor-microenvironment derived effects on Wnt/β-catenin signalling and invasiveness of colorectal cancer cells*", supervisor Prof.dr. Riccardo Fodde |
| 2006 | Short lab rotations<br>Department of Cell Biology, supervisor Prof.dr. Elaine Dzierzak<br>Department of Experimental Pathology, supervisor Dr. Ron Smits |
| 2003-2007 | Medicine study, Erasmus MC, University Medical Center, Rotterdam |
| 2004-2007 | Doctoral exam (*cum laude*) |
| 2003-2004 | Propaedeutic exam |
| 1997-2003 | Gymnasium, Pontes Scholengemeenschap, Locatie Het Goese Lyceum, Goes |
| 2003 | Voorbereidend Wetenschappelijk onderwijs (VWO) exam (*cum laude*) |
| 1990-1997 | Primary education in Germany and The Netherlands |

## *Curriculum Vitae*

Tahsin Stefan Barakat was born on the 25th May of 1984 in Meerbusch, West-Germany. After primary school in Germany and The Netherlands, he graduated *cum laude* for his *Voorbereidend Wetenschappelijk Onderwijs (VWO)* exam in 2003 at the *Pontes Scholengemeenschap, Locatie Het Goese Lyceum*, Goes. In 2003 he started his medical study at the Erasmus MC / Erasmus University, Rotterdam. In 2004 he graduated for his Propaedeutic exam, and was elected for the Master of Science in Molecular Medicine programme at the Erasmus MC. After following several courses belonging to the programme, he performed in 2006 short laboratory rotations at the Departments of Cell Biology (Prof.dr. Elaine Dzierzak) and Experimental Pathology (Dr. Ron Smits). In 2007 he performed a six month research project at the Department of Experimental Pathology under supervision of Prof.dr. Riccardo Fodde, entitled *Characterization of tumor-microenvironment derived effects on Wnt/β-catenin signalling and invasiveness of colorectal cancer cells.* In 2007 he graduated for his Medical Doctoral exam (*cum laude*). From September 2007 until summer 2008 he was at the Department of Reproduction and Development under supervision of Dr. Joost Gribnau, were he performed the studies described in his Master Thesis, entitled *Searching for an X-linked activator of X chromosome inactivation.* From 2008 onwards, he continued his research in the same laboratory as a PhD student, performing the studies described in this thesis, with Prof.dr. J.Anton Grootegoed and Prof.dr. Joost Gribnau as promotors. In July 2012, he visited the laboratory of Prof.dr. Edith Heard in Paris, to perform FISH experiments on post-implantation embryos. After his public thesis defence in September 2012, he will continue his medical study with the clinical internships to obtain the degree of Medical Doctor, to be followed by a further scientific research career as a post-doctoral fellow.

# List of publications

1. Iris Jonkers*, **Tahsin Stefan Barakat***, Eskeatnaf Mulugeta Achame, Kim Monkhorst, Annegien Kenter, Eveline Rentmeester, Frank Grosveld, J. Anton Grootegoed and Joost Gribnau (2009) "RNF12 is an X-Encoded dose-dependent activator of X chromosome inactivation" *Cell* 139(5):999-1011
   * both authors contributed equally
2. **Tahsin Stefan Barakat**, Iris Jonkers, Kim Monkhorst and Joost Gribnau (2010) "X-changing information on X inactivation" *Exp Cell Res* 10;316(5):679-87
3. Christa Buecker, Hsu-Hsin Chen, Jose Maria Polo, Laurence Daheron, Lei Bu, **Tahsin Stefan Barakat**, Patricia Okwieka, Andrew Porter, Joost Gribnau, Konrad Hochedlinger, and Niels Geijsen (2010) "A murine ESC-like state facilitates transgenesis and homologous recombination in human pluripotent stem cells" *Cell Stem Cell* 6:535-46.
4. **Tahsin Stefan Barakat** and Joost Gribnau (2010) "X chromosome inactivation and embryonic stem cells" *Adv Exp Med Biol* 695: 132-154.
5. **Tahsin Stefan Barakat**, Nilhan Gunhanlar, Cristina Gontan Pardo, Eskeatnaf Mulugeta Achame, Mehrnaz Ghazvini, Ruben Boers, Annegien Kenter, Eveline Rentmeester, J.Anton Grootegoed and Joost Gribnau (2011) "RNF12 activates *Xist* and is essential for X chromosome inactivation" *PLoS Genet.* 2011;7(1):e1002001
6. **Tahsin Stefan Barakat**, Eveline Rentmeester, Frank Sleutels, J. Anton Grootegoed and Joost Gribnau (2011) "Precise BAC targeting of genetically polymorphic mouse ES cells" *Nucleic Acids Res* 2011 Oct;39(18):e121
7. Long Zhang, Huizhe Huang, Fang Fang Zhou, Joost Schimmel, Cristina Gontan Pardo, Tingting Zhang, **Tahsin Stefan Barakat**, Kelly-Ann Sheppard, Craig Mickanin, Jeff A. Porter, Alfred C.O. Vertegaal, Hans van Dam, Joost Gribnau, Chris X. Lu, and Peter ten Dijke (2012) "RNF12 Controls Embryonic Stem Cell Fate and Morphogenesis in Zebrafish Embryos by Targeting SMAD7 for Degradation" *Mol Cell* 46:650-61.
8. Cristina Gontan, Eskeatnaf Mulugeta Achame, Jeroen Demmers, **Tahsin Stefan Barakat**, Eveline Rentmeester, Wilfred van IJcken, J. Anton Grootegoed and Joost Gribnau (2012) "RNF12 initiates X chromosome inactivation by targeting REX1 for degradation" *Nature* 2012 **485**(7398): p. 386-90
9. **Tahsin Stefan Barakat** and Joost Gribnau (2012) "X chromosome inactivation in the cycle of life" *Development* 139 (12): 2085-2089
10. **Tahsin Stefan Barakat** and Joost Gribnau (2012) "A Restriction Fragment Length Polymorphism based Bacterial Artificial Chromosome targeting strategy for efficient and fast generation of knockout alleles in polymorphic mouse Embryonic Stem cells" (*Manuscript in preparation*)
11. Erwin Brosens, Elisabeth M. de Jong, **Tahsin Stefan Barakat**, Bert H Eussen, Barbara D'haene, Elfride de Baere, Pino P Poddighe, Robert-Jan Galjaard, Joost Gribnau, Alice S Brooks, Dick Tibboel, and Annelies de Klein (2012) "Congenital malformations of the gastro-intestinal tract and Triple X syndrome" *(Submitted)*

12. **Tahsin Stefan Barakat**, Selma van Staveren, Friedemann Loos, Elvira Myronova, Mehrnaz Ghazvini, J. Anton Grootegoed and Joost Gribnau (2012) "Initiation of X inactivation is regulated by *trans*-acting activators and *cis*-acting elements: no evidence for a functional involvement of X-pairing" *(Submitted)*

# *PhD portfolio*

**General Academic Skills:**
From Development to Disease course, 2009
Article 9 Animal Experimentation course, 2010

**Presentations:**

**2009**
BSIK Stem Cells in Development and Disease Conference, Rotterdam
7th Winter School of the International Graduiertenkolleg, Kleinwalsertal, Austria
2nd Dutch Stem Cell Meeting, Rotterdam
1st Erasmus Stem Cell Institute (ESI) meeting, Rotterdam
16th MGC PhD Student Workshop, Brugge, Belgium (Best Oral Presentation)
3rd SCDD International Symposium "Stem Cells, Development and Regulation" Amsterdam

**2010**
8th Winter School of the International Graduiertenkolleg, Kleinwalsertal, Austria

**2011**
Winter Symposium, "Epigenetics in Development and Disease", Miami, United States of America
4th Dutch Stem Cell Meeting, Leiden
18th MGC PhD Student Workshop, Maastricht
3rd X inactivation Conference, "50 years of X inactivation research", EMBO-workshop, Oxford, United Kingdom

**2012**
2nd Winter School of the Collaborative Research Center (TRR 81), "Chromatin Changes in Differentiation and Malignancies", Kleinwalsertal, Austria
Paris-Rotterdam X chromosome inactivation meeting, Spetses, Greece
10th Annual meeting of the International Society for Stem Cell Research (ISSCR), Yokohama, Japan

**Awards:**

Travel grant of the International Society for Stem Cell Research (ISSCR) for the 10th Annual meeting in Yokohama, Japan, 2012

**International seminars, workshops and conferences:**

**2008**
Stem Cell Symposium, "Stem Cell, Development and Regulation", Amsterdam

**2009**
European Molecular Biology Organisation (EMBO) meeting, Amsterdam
MGC day 2009, Rotterdam
Stem Cell Symposium, "Stem Cell, Development and Regulation", Amsterdam
JNI Symposium, "The stem of cancer", Rotterdam

**2010**
Epigenome Network of Excellence meeting: "Imprinting and X inactivation", Emmetten, Switserland
3rd Dutch Stem Cell meeting, Utrecht
Erasmus Stem Cell Institute Opening Symposium, Rotterdam (poster contribution)
Stem Cell Symposium, "Stem Cell, Development and Regulation", Amsterdam
8th Annual Meeting of the International Society for Stem Cell Research (ISSCR), San Francisco, United States of America

**2011**
6th International meeting, Stem Cell Network North-Rhine-Westphalia, Essen, Germany (Poster contribution)
International Symposium "Chromatin Changes in Differentiation and Malignancies", Giessen, Germany (Poster contribution)

**Teaching activities:**

Junior Science Program:
Supervision lab rotation Junior Science program, October 2009
Supervision Profielwerkstuk Junior Science student 2010-2011

Teaching Medical Curriculum Erasmus MC:
Course "Development of internal and external genitalia", November 2008
Course "Development of internal and external genitalia", December 2009
Course "Early embryos, cloning and transgenesis" November 2010
Course Embryology 2nd year Medicine/Master of Science programme, January 2010

Master of Science in Molecular Medicine Program:
Supervision lab rotation MSc Mol Med student, February 2009
Supervision lab rotation MSc Mol Med student, October 2009
Supervision lab rotation MSc Mol Med student, January 2010
Supervision MSc Thesis Selma van Staveren, "Initiation of X chromosome Inactivation" 2010-2011
Supervision MSc Thesis Elvira Myronova, 2011-2012

# Acknowledgements

Finally, after a long journey, I'm arriving at the finish. For sure it has been a long journey, in which I travelled approximately 516780 km or 12.9 times around the earth; that's the distance you travel if you live in Zeeland and study and work in Rotterdam, during 5 years of study and 4 years of PhD. If I just look back at the last 4 years, many things have happened during that period, here just a small selection of the "really important" things:

The layout of the faculty changed completely and we also changed a bit the view on X chromosome inactivation; unnecessary wars have unfortunately been characterizing the politics in the world, we arrived in a economical crisis, the 7 billions human being has been born, a mad person with colored hair tried to come up for the rights of *Henk* and *Ingrid* in Dutch politics, but instead yet another round of new elections is upcoming. A nuclear catastrophe was necessary to finally result in a different view on nuclear energy. And two Olympic Games and several football tournaments passed by, with the only constant being that in every important football match I look at, my favorite team does not win.

So a lot has happened and changed in the world, and for sure also I changed due to the many positive but sometimes also negative events which happened during this journey. I came across many people during that exciting trip, and to all of them I would like to say thank you!

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I was lucky to get a lot of help from several talented Master students. Nilhan, although you were not my student, I saw you often passing by with that one famous question of you ("I have a question"). It was always fun answering them, and it was really nice to start to collaborate even more at the end of your project. Good luck with your own PhD! Selma! Mijn eerste "echte" student! Het was erg bijzonder om jouw begeleider te zijn. Ik zal maar niet weer over de generatiekloof beginnen... Wat heb ik met jou gelachen! Het was heel erg indrukwekkend wat je allemaal in een jaar gedaan hebt, en het was een groot plezier om met jou samen te werken. Op een gegeven moment konden we elkaar echt blind begrijpen, en ook buiten het werk om hadden we snel een goede draad gevonden. Het was en is een plezier! Veel succes met je co-schappen, waarin je nu mijn voorbeeld kunt zijn. Elvira, mijn tweede student! Jij bent compleet anders, maar toch niet minder leuk! Het duurde even een beetje voordat ik doorhad hoe jij werkt, maar ook met jou heb ik vele grappige momenten meegemaakt, die ik niet zou willen missen. Bedankt voor al je hulp, en succes voor je toekomst! Selma en Elvira, jullie ook nog een keer beiden bedankt voor het feit dat jullie mij ook tijdens mijn verdediging als Paranimfen bijstaan, ik ben trots op jullie!

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Of course, the Erasmus MC is larger then only lab 9.02. One social meeting club is for sure the 10th floor (cell culture), where I met many nice persons. Fanny, thanks for the many nice things we did together at the start of our PhDs. I still didn't manage to convince you that there is nice weather in the Netherlands. Let's meet again soon! Gerben, dank je voor je gezelligheid en al je adviezen over spiercellen. Vind het nog steeds heel grappig dat we door een toevalsbevinding nu zelfs een collaboratie hebben, en natuurlijk, speciale dank voor de kooien, je weet waar ik het over heb... Alvin, ook jij maakt de celkweek tot een special environment. Also all the others, you are special as well: Polynikis, Parham, Thomas, Jessica, Carol, Jean-Charles, Catherine R, Dorota, Derk, Frank S, Parissa, Melodi, Jeffrey, Reinier, Siska, Dies, and Elaine. Also in the rest of the building, I found many nice people: Xiao, Tiana, Katharina amongst many others. Sahar (icecream), good luck in Amsterdam! Sabrina, viel Erfolg mit Deinem Medizin Studium! Bin mir sicher Du meisterst es mit Bravour! En ook niet onbelangrijk, Ron Smits, dank je dat je mij hebt leren pipetteren!

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Tahsin Stefan Barakat, August 2012