

Genetic Engineering

Volume 1

Principles, Mechanism, and Expression



Tariq Ahmad Bhat | Jameel M. Al-Khayri
Editors



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Volume 1

Principles, Mechanism, and Expression

Edited by

Tariq Ahmad Bhat, PhD

Jameel M. Al-Khayri, PhD



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Dedication

This book is dedicated to:



Fatima bint Muhammad Al-Fihriya Al-Qurashiya

An Arab Muslim woman who is attributed with founding the oldest existing and continually operating, and first degree-awarding educational institution for natural sciences in the world, the University of al-Qarawiyyin Fez, Morocco, in 859 CE, she is also known as “Umm al-Banīn.”

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About the Editors



Tariq Ahmad Bhat, PhD

*Lecturer on Botany, Department of Education,
Govt. of Jammu and Kashmir, India*

Tariq Ahmad Bhat, PhD, with 18 years of teaching experience, is a lecturer on botany in the Department of Education, Govt. of Jammu and Kashmir, India, and is engaged in active research of molecular biology, cell biology, mutation breeding, and genetic improvement of legumes and medicinal plants. He has published 10 international books, 90 research papers, review articles, and book chapters. He has participated in 50 conferences, training programs, and workshops. He is one of the founder faculty members of the Chief Minister's Super 50 NEET Programme in Jammu and Kashmir, India. He is serving as the District Coordinator Anantnag of a prestigious project on medicinal plants under financial assistance of the National Medicinal Plants Board (NMPB), New Delhi (Ministry of AYUSH), India. The Government of India conferred on him the Best innovative Science Teacher Award 2014 in recognition of his meritorious services. Dr. Bhat has received his MSc and PhD from AMU, Aligarh India.



Jameel M. Al-Khayri, PhD

*Professor of Plant Biotechnology,
Department of Agricultural Biotechnology,
College of Agriculture and Food Sciences,
King Faisal University, Saudi Arabia*

Jameel M. Al-Khayri, PhD, is Professor of Plant Biotechnology at the Department of Agricultural Biotechnology, College of Agriculture and Food Sciences, King Faisal University, Saudi Arabia.

He has dedicated his research efforts on date palm biotechnology for the last three decades. He has published over 60 research articles and reviews in international journals in addition to 30 book chapters. Dr. Al-Khayri is editor of several special issues of international journals on date palm, biotechnology, and sustainable agriculture under abiotic and biotic stress. He is editor of 15 Springer reference books, including *Date Palm Biotechnology*, *Date Palm Genetic Resources and Utilization* (2 volumes), *Date Palm Biotechnology Protocols* (2 volumes), and *Advances in Plant Breeding Strategies* (9 volumes). He is a member of the editorial board and reviewers' panels of several international journals. He has participated in the organizing and scientific committees of international scientific conferences and contributed over 50 research presentations. In addition to teaching, graduate students advising, and conducting funded research projects, he has held administrative posts as Assistant Director of the Date Palm Research Center, Head of Department of Plant Biotechnology, and Vice Dean for Development and Quality Assurance. Dr. Al-Khayri is an active member of the International Society for Horticultural Science and the Society for In Vitro Biology and serves as the National Correspondent of the International Association of Plant Tissue Culture and Biotechnology. He served as a member of Majlis Ash-Shura (Saudi Arabia Legislative Council) Fifth Session. Currently, he maintains an active research program on date palm focusing on genetic transformation, secondary metabolites, and in vitro mutagenesis to enhance tolerance to abiotic and biotic stress. He is interested in the role of biotechnology in enhancing food security and the impact of global climate change on agriculture. Dr. Al-Khayri earned a BS in Biology from the University of Toledo and an MS in Agronomy and PhD in Plant Science from the University of Arkansas, USA.

Contents

<i>Contributors</i>	<i>xi</i>
<i>Abbreviations</i>	<i>xv</i>
<i>Acknowledgment</i>	<i>xix</i>
<i>Foreword</i>	<i>xxi</i>
<i>Preface</i>	<i>xxiii</i>
1. Concepts of Genetic Engineering	1
Mohammad Amin Lone and Anzar A. Shah	
2. Enzymes of Genetic Engineering	23
Ahmad Ali and Johra Khan	
3. Tools Used in Genetic Engineering	45
Ankita Sharma, Ahmad Ali, and Johra Khan	
4. Introduction of Recombinant DNA into Host Cells	77
Rida Saleem, Sitara Nasar, and Saima Iftikhar	
5. Linking of Desired Gene with DNA Vector/Gene Cloning Vector	97
Sitara Nasar and Saima Iftikhar	
6. Polymerase Chain Reaction	119
Asima Tayyeb and Zhuha Basit	
7. Concept and Nature of Genes	147
Anjum Sabba and Najeebul Tarfeen	
8. Blotting Techniques	169
Asima Tayyeb, Zhuha Basit, and Hanfa Ashfaq	
9. Chromosome Jumping	189
Muhammad Ishtiaq, Mahnoor Muzammil, and Mehwish Maqbool	
10. Electrophoresis	199
Muhammad Ishtiaq, Mahnoor Muzammil, and Mehwish Maqbool	

11. Genetically Engineered Microorganisms.....	219
Krina Mehta, Rohit Patel, Sameera Sharma, Arpit Shukla, Dweipayan Goswami, Meenu Saraf, and Paritosh Parmar	
12. Molecular Markers and Their Applications.....	251
Abdul Rehman, Hafiza Iqra Almas, Abdul Qayyum, Hongge Li, Zhen Peng, Guangyong Qin, Yinhua Jia, Zhaoe Pan, Shoupu He, and Xiongming Du	
<i>Index</i>.....	285

Contributors

Ahmad Ali

Department of Life Sciences, University of Mumbai, Vidyanagari, Santacruz (E), Mumbai, Maharashtra, India

Hafiza Iqra Almas

Department of Botany, University of Agriculture, Faisalabad, Pakistan

Hanfa Ashfaq

School of Biological Sciences, University of the Punjab, Lahore, Pakistan

Zhuha Basit

School of Biological Sciences, University of the Punjab, Lahore, Pakistan

Xiongming Du

Zhengzhou Research Base, State Key Laboratory of Cotton Biology, Zhengzhou University, Zhengzhou, China

Dweipayan Goswami

Department of Microbiology and Biotechnology, Gujarat University, Ahmedabad, Gujarat, India

Shoupu He

Zhengzhou Research Base, State Key Laboratory of Cotton Biology, Zhengzhou University, Zhengzhou, China

Saima Iftikhar

School of Biological Sciences, University of the Punjab, Lahore, Pakistan

Muhammad Ishtiaq

Department of Botany, Mirpur University of Science and Technology (MUST), Mirpur, Azad Jammu and Kashmir (AJK), Pakistan

Yinhua Jia

State Key Laboratory of Cotton Biology, Institute of Cotton Research, Chinese Academy of Agricultural Science, Anyang, Henan, China

Johra Khan

Department of Medical Laboratory Sciences, College of Applied Medical Sciences, Majmaah University, Majmaah, Saudi Arabia

Hongge Li

State Key Laboratory of Cotton Biology, Institute of Cotton Research, Chinese Academy of Agricultural Science, Anyang, Henan, China

Mohammad Amin Lone

Department of Zoology, Government Degree College, Uri, Jammu and Kashmir, India

Mehwish Maqbool

Department of Botany, Mirpur University of Science and Technology (MUST), Mirpur, Azad Jammu and Kashmir (AJK), Pakistan

Krina Mehta

Department of Microbiology and Biotechnology, Gujarat University, Ahmedabad, Gujarat, India

Mahnoor Muzammil

Department of Botany, Mirpur University of Science and Technology (MUST), Mirpur, Azad Jammu and Kashmir (AJK), Pakistan

Najeebul Tarfeen

Center for Research and Development (CORD), University of Kashmir, Hazratbal, Srinagar, Jammu and Kashmir, India

Sitara Nasar

School of Biological Sciences, University of the Punjab, Lahore, Pakistan

Zhaoe Pan

State Key Laboratory of Cotton Biology, Institute of Cotton Research, Chinese Academy of Agricultural Science, Anyang, Henan, China

Paritosh Parmar

Department of Biotechnology and Bioengineering, Institute of Advanced Research, Koba Institutional Area, Gandhinagar, Gujarat, India

Rohit Patel

Department of Microbiology and Biotechnology, Gujarat University, Ahmedabad, Gujarat, India

Zhen Peng

State Key Laboratory of Cotton Biology, Institute of Cotton Research, Chinese Academy of Agricultural Science, Anyang, Henan, China

Abdul Qayyum

Department of Plant Breeding and Genetics, Bahauddin Zakariya University, Multan, Pakistan

Guangyong Qin

Zhengzhou Research Base, State Key Laboratory of Cotton Biology, Zhengzhou University, Zhengzhou, China

Abdul Rehman

Zhengzhou Research Base, State Key Laboratory of Cotton Biology, Zhengzhou University, Zhengzhou, China

Rida Saleem

School of Biological Sciences, University of the Punjab, Lahore, Pakistan

Anjum Sabba

Department of Biochemistry, University of Kashmir, Hazratbal, Srinagar, Jammu and Kashmir, India

Meenu Saraf

Department of Microbiology and Biotechnology, Gujarat University, Ahmedabad, Gujarat, India

Anzar A. Shah

Department of Zoology, Government Degree College, Uri, Jammu and Kashmir, India

Ankita Sharma

Department of Life Sciences, University of Mumbai, Vidyanagari, Santacruz (E), Mumbai, Maharashtra, India

Sameera Sharma

Department of Microbiology and Biotechnology, Gujarat University, Ahmedabad, Gujarat, India

Arpit Shukla

Department of Biological Sciences and Biotechnology, Institute of Advanced Research,
University of Innovation, Koba Institutional Area, Gandhinagar, Gujarat, India

Asima Tayyeb

School of Biological Sciences, University of the Punjab, Lahore, Pakistan



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Abbreviations

A	adenine
ADA	adenosine deaminase
AFLP	amplified fragment length polymorphism
Ald	α -acetolactate decarboxylase
ALP	alkaline phosphatase
AMV	avian myeloblastosis virus
ARMS	amplification refractory mutation system
ARS	autonomously replicating sequence
BACs	bacterial artificial chromosomes
BSA	bovine serum albumin
Bst	<i>Bacillus stearothermophilus</i>
C	cytosine
CarE B1	carboxylesterase B1
CCCP	carbonyl cyanide m-chlorophenyl hydrazone
cDNA	complementary DNA
CE	capillary electrophoresis
CRISPR	clustered regularly interspaced short palindromic repeats
CSF	cerebrospinal fluids
CVS	chorionic villus sampling
DB 71	direct blue 71
DEAE-dextran	diethylaminoethyl-dextran
DGGE	denaturing gradient gel electrophoresis
D-LDH	d-lactate dehydrogenase
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid

DNase I	deoxyribonuclease I
dNTPs	deoxyribonucleoside triphosphates
DOPE	dioleylphosphatidyl ethanolamine
Dr	diacetyl reductase
dsDNA	double-stranded DNA
E. coli	Escherichia coli
EDTA	ethylene-diamine-tetraacetate
ELOSA	enzyme-linked oligonucleotide sorbent assay
EMF	electromotive force
ER	endonucleases
FBrAtio	flux balance analysis with flux ratios
FDA	Food and Drug Administration
FO	function oxidases
FRET	fluorescence resonance energy transfer
G	guanine
GE	genetically engineered
GEM	genetically engineered microorganisms
GEMs	genetically engineered microbes
GLP-1	glucagon-like peptide 1
GM	genetically modified
GMO	genetically modified organisms
GRAS	generally recognized as safe
GST	glutathione S-transferases
GTS	genomic template stability
HBV	hepatitis B virus
HFCS	high-fructose corn syrup
HFD	high-fat diet
HGT	horizontal gene transfer
HPCE	high-performance capillary electrophoresis

HPLC	high-performance liquid chromatography
HSV	herpes simplex virus
HTML-PCR	homopolymer tail-mediated ligation PCR
IEF	isoelectric focusing
IPTG	isopropyl β -d-1-thiogalactopyranoside
ITP	isotachopheresis
LAB	lactic acid bacteria
Ldh	lactate dehydrogenase
LIF	laser-induced fluorescence
lncRNA	long non-coding RNA
LTRs	long terminal repeats
MAB	marker-assisted breeding
MAC	mammalian artificial chromosome
MCE	microchip electrophoresis
MCF	microbial cell factories
MCS	multiple cloning site
MFO	mixed function oxidases
mpd	methyl parathion hydrolase gene
MT	metallothionein
OP	organophosphorus
ORF	open reading frames
Ori	origin of replication
PACs	P1-derived artificial chromosomes
PAGE	polyacrylamide gel electrophoresis
PAR α	proliferator-activated receptors α
PCR	polymerase chain reaction
PFE	pulsed-field gel electrophoresis
pHSA	plasma HSA
Pnk	polynucleotide kinase

PNP	p-nitrophenol
PPAR α	proliferator-activated receptors α
PTM	post-translational modifications
PVDF	polyvinylidene fluoride
pytH	pyrethroid hydrolase gene
QS	quorum sensing
rDNA	recombinant DNA
RFLP	restriction fragment length polymorphism
rHSA	recombinant HSA
RM	restriction/modification
RNA	ribonucleic acid
RT	real-time
RT-PCR	reverse transcriptase PCR
SDS	sodium dodecyl sulfate
SDS-PAGE	sodium dodecyl sulfate-polyacrylamide gel electrophoresis
SNP	single nucleotide polymorphism
sRNA	small regulatory RNAs
SSC	saline-sodium citrate
ST	S-transferases
T	thymine
TAE	tris/acetate/EDTA
YAC	yeast artificial chromosome

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Foreword

Genetic engineering is the science of manipulating the genetic material of an organism. The first artificial genetic modification accomplished by Herbert Boyer and Stanley Cohen in 1973 was the result of a series of advancements in techniques that allowed the direct modification of the genome by transferring genetic information from one organism to the other. Important advances included the discovery of restriction enzymes by Werner Arber and Hamilton O. Smith in the 1970s and DNA ligases by combined efforts of Gellert, Lehman, Richardson, and Jerard Hurwitz in the 1960s and early 1970s, the ability to design plasmids, and technologies like polymerase chain reaction (PCR) by Kary Mullis in 1983, and DNA sequencing by Frederick Sanger, Walter Gilbert, Allan Maxam in 1977 and John Craig Venter in 1999.

Several other discoveries and developments that occurred later brought this technology of genetic engineering to the level that we see today. From 1990 to 2003, the Human Genome Project succeeded in mapping the human genome with more than 20,000 genes identified and their genomic loci documented. Dolly was cloned under the leadership of Ian Wilmut in 1996. Transformation of the DNA into a host organism was accomplished with the invention of biolistics, agrobacterium-mediated recombination, and microinjection. The first genetically modified (GM) animal was a mouse created in 1974 by Rudolf Jaenisch. In 1976 the technology was commercialized, with the advent of genetically modified bacteria that produced somatostatin, followed by insulin in 1978. In 1983 an antibiotic-resistant gene was inserted into tobacco, leading to the first genetically engineered (GE) plant.

Advances followed that allowed scientists to manipulate and add genes to a variety of different organisms and induce a range of different effects. Plants were first commercialized with virus-resistant tobacco released in China in 1992. The first genetically modified food was the Flavr Savr tomato, marketed in 1994. By 2010, 29 countries had planted commercialized biotech crops. In 2000 a paper published in *Science* introduced golden rice, the first food developed with increased nutrient value.

In the present decade of 2010–2020, the development therapies that have been theorized and studied for years are finally being approved for humans, as the discovery of CRISPR, possibly the greatest achievement in the history of genetics, takes hold in the world.

Volume 1 of this book, *Genetic Engineering*, encompasses all the basic concepts of the various components of recombinant DNA (rDNA) technology. The book has been designed to communicate the fundamental principles of genetic engineering through an explanation of various molecular biology phenomena and the development of various technologies over the years. The various chapters have been written by young and experienced experts in their respective fields from different elite educational institutions across the globe. I applaud the editor, Dr. Tariq Ahmad Bhat, as well as the book chapter contributors for successfully bringing together this volume.

—**Abdul Rauf Shakoori**
*Distinguished National Professor,
Professor Emeritus,
University of the Punjab, Lahore, Pakistan*

Preface

The advent of biotechnology has forever changed human perception of living entities. Genetic engineering enables the precise control of the genetic composition and gene expression of organisms directed toward the advantage of human well-being. Innovative applications have emerged in environmental sustainability, food and nutritional security, and medicinal advancement. The utilization of this powerful technology solicits contrasting opinions among scientists, politicians, and the public in relation to biosafety and bioethics. This necessitated the engagement in research aimed at understanding the safety of genetic engineering products and prompted the development of national and international policies. This book addresses these aspects in two volumes: *Volume 1, Genetic Engineering: Principles, Mechanism, and Expression*, and *Volume 2, Genetic Engineering: Applications, Bioethics, and Biosafety*.

Volume 1 consists of 12 chapters covering genetic engineering concepts, molecular tools, and technologies utilized in the manipulation, amplification, and introgression of DNA. Topics covered are concepts of genetic engineering, enzymes of genetic engineering, tools used in genetic engineering, the introduction of recombinant DNA (rDNA) into host cells, linking of the desired gene with DNA vector/gene cloning vector, polymerase chain reaction (PCR), concept and nature of genes, blotting techniques, chromosome jumping, electrophoresis, genetically engineered (GE) microorganisms, and molecular markers and their applications.

This book is a valuable asset to upper-undergraduate and postgraduate students, teachers, and researchers interested in cell biology, genetics, molecular genetics, biochemistry, biotechnology, botany, zoology, and agriculture sciences. The chapters are contributed by experts in their fields, presenting recent contemporary developments in genetic engineering research supported with illustrations, tables, and recent references. We are thankful to all the authors across the globe who contributed their research output in the form of book chapters to make our project a successful endeavor. We wish to present our gratitude to the contributing authors for their generous cooperation and to Apple Academic Press (AAP)/CRC

Press/Taylor and Francis Group for giving us the opportunity to publish this work.

—**Tariq Ahmad Bhat, PhD**
Jammu and Kashmir, India

Jameel M. Al-Khayri, PhD
Al-Ahsa, Saudi Arabia

CHAPTER 1

Concepts of Genetic Engineering

MOHAMMAD AMIN LONE and ANZAR A. SHAH

Department of Zoology, Government Degree College, Uri, Jammu and Kashmir, India

ABSTRACT

Genetic engineering, also known as gene modification or gene editing, is a field of biotechnology that involves the direct manipulation of an organism's genetic material in order to modify or add traits. This can be done through a variety of techniques, such as the insertion of genetically modified DNA into an organism, or the disruption or suppression of certain genes. Genetic engineering has the potential to revolutionize the way we produce food, create new medicines, and address environmental challenges. However, it is also a controversial field, with many ethical, social, and environmental considerations.

One of the key concepts in genetic engineering is the use of genetically modified organisms (GMOs). These are organisms whose genetic material has been modified using genetic engineering techniques. The goal of using GMOs is often to introduce new traits or characteristics into the organism, such as increased resistance to pests or diseases, or enhanced nutritional value. However, there are concerns about the safety of GMOs, both for the environment and for human consumption.

Another important concept in genetic engineering is gene editing, which involves the precise modification of an organism's genetic material at the DNA level. Gene editing has the potential to be used for a wide

range of applications, including the treatment of genetic diseases and the production of new medicines. However, there are also concerns about the potential ethical implications of gene editing, such as the creation of designer babies or the enhancement of human traits.

Overall, genetic engineering is a complex and rapidly-evolving field with the potential to significantly impact many aspects of our lives. While it offers many benefits, it also raises important ethical, social, and environmental considerations that need to be carefully considered as the field continues to develop.

1.1 HISTORICAL PERCEPTIVE OF GENETIC ENGINEERING

The structural elucidation of genetic material and code marked a new dawn in the field of science. It became very evident that genetic material conceals numerous biological secrets inside, which were yet to be explored. Post-1970s led to huge technological advancement, which paved the way towards new analysis and manipulation in genetic material. Consequently, many breakthroughs were achieved after the detailed structure of DNA and RNA was documented. It was only after World War II, people mainly biologists and philosophers began to analyze a growing link between biology and technology. Eventually, a new field of science which could be used for the improvisation of human life evolved as genetic engineering. The idea of changing the human nature may thus benefit the society. It was only after Second World War, scientists began to institutionalize biology and technology by establishing new departments, institutes, and ministries. Thus, with the new advances in the field of molecular biology, genetic engineering became more of science than merely an art.

The concept of genetic engineering dates long before the structural documentation of DNA and RNA. However, the expression “genetic engineering” was first used by the science-fiction novelist but not by scientist. It was in 1951; Jack Williamson used the term “genetic engineering” in his novel “Dragon’s Island” (Williamson, 2012).

People around the globe were already familiar with the art of using living micro-organisms to manufacture new products. The best example in this regard is the process of fermentation, where ancient people utilized the service of living micro-organisms to get new and improved products such as bread and alcohol. As the events progressed, knowledge of protein

synthesis from regions of deoxyribonucleic acid (DNA) (called genes) provided a key to in-depth exploration in the DNA structural base.

With plenty of exploration and subsequent advancement of new genetic techniques, expression of gene was made conceivable regardless of its origin, in a simple micro-organism like *Escherichia coli* (*E. coli*) leading to the increased production of the product coded by that gene. Based on the same principle, vast number of other organisms both micro and macro were used to get efficient and large quantity of products. It was only before 1990 a new technique namely protein engineering became possible as a new outcome of genetic engineering (Maloy & Hughes, 2013). With the course of time, new discoveries and advancements came into existence which changed the whole scenario of the scientific world. It was Karl Ereky who specified a whole new subject as biotechnology (Fári & Kralovánszky, 2006). It is very important to mention that the term genetic engineering was coined in 1940 by A Jost. However, the most important discovery in the arena was that of enzymes and vectors. These two together changed the whole concept of biology and hence marked the beginning of a new dawn in the scientific world.

1.2 KEY CONCEPTS IN GENETIC ENGINEERING

1.2.1 GENE

Gene is the basic physical, structural, and functional unit of inheritance which occupies a fixed place on a chromosome. It may be chemically defined as a sequence of nucleotides carrying specific hereditary information (Pearson, 2006). More specifically, it is the nucleic acid DNA or RNA which codes the synthesis of the gene product, whether it is RNA or protein (Morange, 2000).

1.2.2 RECOMBINANT DNA (RDNA)

Recombinant DNA (rDNA) can be defined as a solitary chimeric DNA produced by joining two or more dissimilar fragments of DNA from different organisms. The technique used to produce rDNA is called rDNA technology. The organism is categorized as donor and host. The donor is the organism from which the isolation of DNA is done and the host is the

organism in which this DNA is incorporated. Paul Berg, Herbert W Boyer, and Stanley N Cohen are the pioneers of rDNA technology. The first ever rDNA molecule was created by recombining the SV40 monkey DNA virus genome and a bacterial virus known as phage λ (Robl, Wang, Kasinathan, & Kuroiwa, 2007).

1.2.3 VECTORS-DELIVERY SYSTEM IN RECOMBINANT DNA (RDNA) TECHNOLOGY

Vectors are important tool in rDNA technology as they act as transporters and thereby work as vehicles which deliver the genetic material in the organism of interest. Vectors may thus be defined autonomously replicating DNA molecule engaged to transport foreign hereditary material to host cells. Vectors are basically transgenic DNA bodies which possess a larger unit as foundation and smaller unit as foreign DNA. The smaller foreign DNA is ultimately expressed in the host cell thereby is transmitted. Vectors are broadly classified into two types, i.e., cloning vector and expression vector. Cloning vector is used to amplify the number of copies of a cloned DNA fragment. However, Expression vector is designed to for expressing foreign gene into a protein.

1.3 PROPERTIES OF AN EFFICIENT AND IDEAL VECTOR

An efficient vector should possess the following properties:

- The first and foremost property which an ideal vector should possess is an autonomous replicating nature which means it should possess Ori (origin of replication) region.
- It should possess at least a selectable marker, e.g., antibiotic resistance marker.
- Should possess a screenable marker/scorable marker. Scorable marker produces an end product which can easily be noticed by means of a simple and quantitative assay. The examples include markers of β -galactosidase, green fluorescent protein, etc.
- Occurrence of unique restriction enzyme site. This is very important as it forms the main criterion for any vector to be used in rDNA technology.

- Should possess several cloning sites.
- Should possibly be small in size and easy to handle.
- Should kick off DNA replication autonomously to get numerous copies.
- Presence of suitable regulatory elements for expressing foreign gene.
- The selection of a suitable vector depends mainly on the size limit of inserted DNA and category of host projected for cloning.

The other classification of vectors is based on its transmitting form and includes synthetic or artificial chromosomes, plasmids, viruses, and cosmids. However, of all four types, the most commonly used vectors include viruses and plasmids. Vectors have the property of being transcribed, translated, inserted, and then expressed.

1.4 PLASMIDS

These vectors include double-stranded spherical DNA having the property of self-replication in the host. They are primarily characteristic of prokaryotes but can also exist in eukaryotes. Because of autonomous self-replicating behavior, they are also known as replicons. Plasmids mainly carry genes for antibiotic resistance which later on acts as marker in rDNA technology. Plasmids are of two types, i.e., integrating plasmids and non-integrating plasmids. As the name specifies, non-integrating plasmids don't unite with the host DNA and replicate autonomously when the host cell divides. However, integrating plasmids amalgamate with the host DNA to get replicated. The size of plasmid ranges from few kbs to 100 kbs. Examples of plasmid vectors include pBR322 and pUC vector (Figure 1.1).

1.5 VIRUSES

Viruses play a key role as carriers and execute this role by *in vivo* and *in vitro* methods. Viruses transfer genes by the process of transduction. Viral vectors are primarily pathogenic but their pathogenicity is minimized by remodeling their genetic structure and by scissoring the gene of replication. These viruses can only infect and can't reproduce rendering them

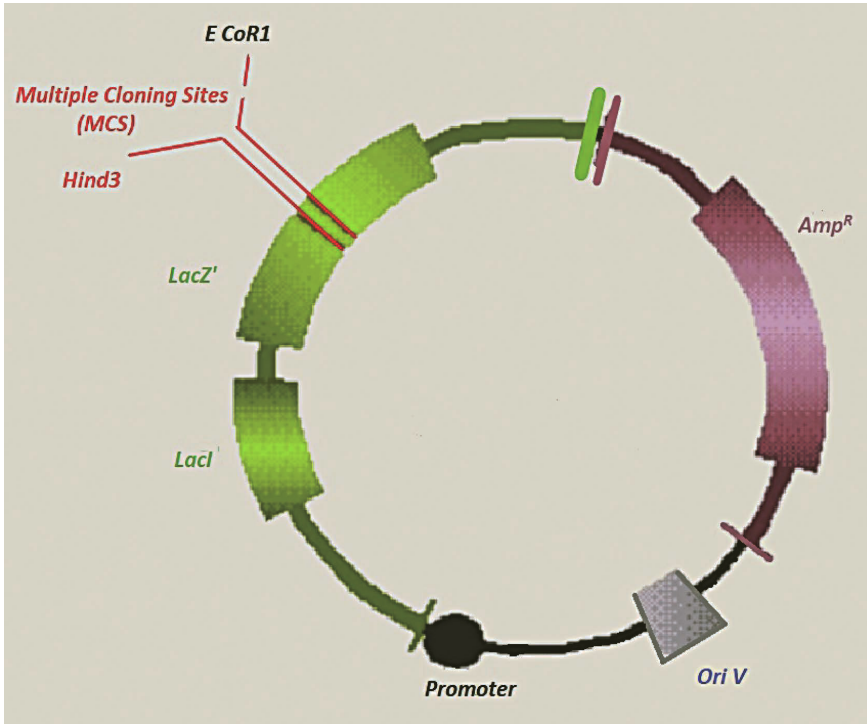


FIGURE 1.1 Diagram showing a plasmid vector construct from the pUC family consisting of ampicillin-resistant gene, promoter, LacI repressor gene, origin of replication LacZ gene for peptide of galactosidase. It also contains multiple cloning regions showing different restriction endonucleases.

harmless. Viruses are very stable and concrete. Viral vectors can infect multiple types of cells thereby are diverse in nature compared to plasmid. Avery, a smaller number of naturally occurring viruses manufacture single-stranded DNA in their life cycle. Examples include M13, fl, and fd and have been manipulated to be suitable vector (Figure 1.2).

1.6 COSMID

The huge drawback of the plasmid vector is its transformation inefficiency of cloning large segments of DNA. In order to overcome this problem, a new type of vector has been designed with high effectiveness compared to the plasmid vector. The cosmid vector is the blend of the plasmid

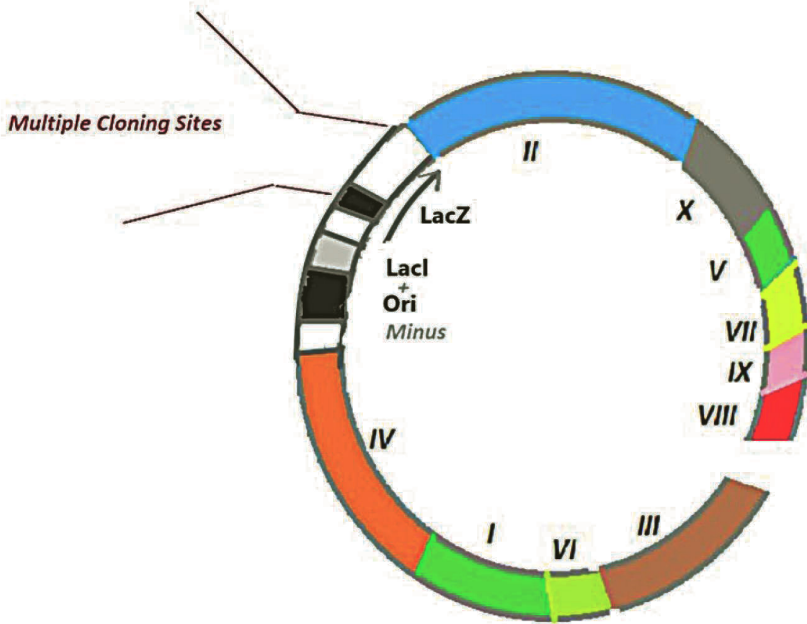


FIGURE 1.2 Diagram showing M13mp18 viral vector showing multiple cloning sites.

vector and the lambda phage *cos* sequence (Hohn & Murray, 1977). These arrangements enable target DNA to be incorporated into the λ head (Chauthaiwale, Therwath, & Deshpande, 1992). They were first described by Collins and Hohn in 1978.

The cosmid vector can hold up to 45 kb of DNA while plasmid and λ phage vectors are limited to 25 kb (Hohn & Murray, 1977).

The main difference compared to usual plasmid vectors is the presence of a small piece of lambda DNA, known as the cohesive end site. Lambda DNA in the virus is linear with two complementary single-stranded ends, therefore, are called the cohesive ends or *cos* sites (Figure 1.3).

1.7 SYNTHETIC OR ARTIFICIAL CHROMOSOMES

These are also cloning vectors that transport larger DNA inserts than plasmids or lambda-phage-derived vectors. Artificial chromosomes contain all

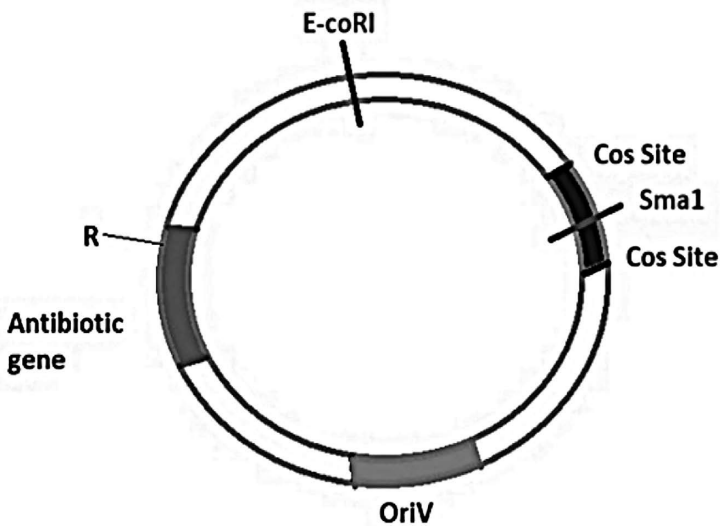


FIGURE 1.3 Diagram showing structure of cosmid vector–plasmid vector + Cos site.

the elements that are critical for replication and stability of the molecule within the host cell (O'Brien & Lummis, 2011). For instance, the first artificial chromosome, known as yeast artificial chromosome (YAC) vectors, is able to bear DNA inserts as huge as 2,000 kb. Similarly, bacterial artificial chromosomes (BACs) and P1-derived Artificial chromosomes (PACs) were designed to address the difficulty of insert chimerism and instability (Robl et al., 2003). Other examples include mammalian artificial chromosomes (MACs) designed for mammalian cells, including human cells (Figure 1.4 and Table 1.1).

1.8 BASIC STEPS REQUIRED IN GENETIC ENGINEERING

1.8.1 ISOLATION OF DNA

Genetic material is contained inside the cells. It has to be obtained in pure form without even the attached histones and other proteins. The first step in DNA purification is to open the cells and release DNA. The method should be gentle to preserve the native DNA; the approaches to break the cells vary due to the variability in the cell structure.

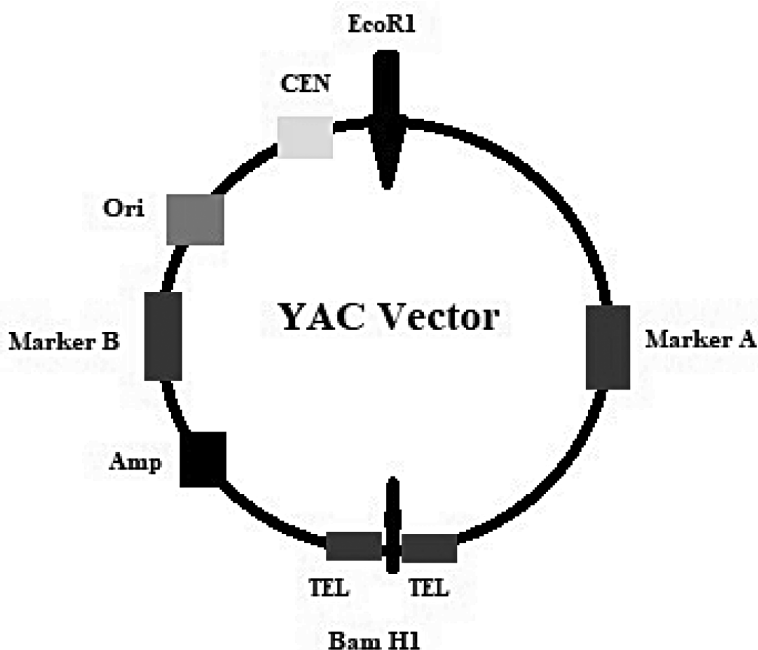


FIGURE 1.4 Diagram showing YAC vector.

TABLE 1.1 Some Milestones in the History of Genetic Engineering

Sl. No.	Year	Event
1.	1917	The term Biotechnology coined by Karl Ereky.
2.	1940	The term Genetic Engineering coined by A. Jost.
3.	1943	Penicillin produced on an industrial scale.
4.	1944	Avery, Macleod, and Mc Carty demonstrated that DNA is the genetic material.
5.	1953	The structure of DNA was determined Watson and Crick.
6.	1958	For studying the primary structure of proteins and genetic recombination in a bacterium F. Sanger, Joshua Lederberg, G.W. Beadle, and Edward L. Tatum were jointly awarded the Noble prize in chemistry and physiology or Medicine.
7.	1959	Arthur Kornberg and Severo Ochoa were awarded the Noble prize for the synthesis of DNA and RNA.
8.	1961–1966	The entire genetic code is deciphered.
9.	1970	The First Restriction endonuclease, Hind II was isolated by Hamilton O. Smith, Thomas Kelly, and Kent Wilcox from the bacterium <i>Haemophilus influenza</i> .

TABLE 1.1 (Continued)

Sl. No.	Year	Event
10.	1973	Boyer and Cohen established recombinant DNA technology.
11.	1974	Rudolf Jaenisch created a genetically modified mouse.
12.	1977	Fredrich sanger developed a method for sequencing DNA.
13.	1978	Genentech produced human insulin in <i>E. coli</i>
14.	1983	PCR developed by Karry Mullis.
15.	1983	An antibiotic-resistant gene was introduced into tobacco, leading to the first genetically modified plant.
16.	1987	Recombinant vaccine for hepatitis B (HBsAg) became the first synthetic vaccine for public use.
17.	1988	PCR method was published.
18.	1990	The human genome was officially initiated.
19.	1994	The first GM food known as FlavrSavr tomato has been commercialized globally. The FDA reports that genetically modified tomatoes are as safe as traditional tomatoes.
20.	1995	The first genome sequence for the bacterium <i>Haemophilus influenza</i> has been completed.
21.	1996	The commercial planting of genetically modified crops has been launched.
22.	1997	India became the fourth country in the world to develop an indigenous hepatitis B vaccine.
23.	1997	The first-ever mammal clone named Dolly was developed by Wilmut and Campbel. Dolly was a sheep with a mother and no father.
24.	2000	GM rice, called golden rice, rich in beta carotene, the precursor of Vitamin A, has been developed.
25.	2001	Human genome is sequenced.

1.8.1.1 LYSIS OF CELLS

The lysis or breakdown of bacterial cells is brought about by the use of an enzyme Lysozyme and the chemical ethylene-diamine-tetraacetate (EDTA) followed by the addition of detergents, namely sodium dodecyl sulfate (SDS).

The lysis of animal cells is directly carried out by treating them with a detergent-like SDS. Plant cells require very harsh treatment to break them

open. Besides the treatment of enzymes like *cellulase* and *pectinase*, the cells are frozen and subsequently crushed in mortar and pestle.

1.8.1.2 PURIFICATION OF DNA

This involves the complete breakdown or removal of all the cellular materials other than DNA. This is achieved by homogenizing and centrifuging the treated cells to break the cells and their nuclear envelopes. The homogenized product is then treated with proteases to digest histones and other proteins; ribonucleases to digest RNA; amylases and lipases to digest polysaccharides and lipids, respectively. DNA remains intact. This DNA is precipitated by adding ethanol. DNA appears as a mass of very fine threads that can be separated by spooling or winding over a fine appliance.

1.8.2 GENERATION OF DNA FRAGMENTS

The desired genes (gene of interest) to be cloned are prepared in three ways:

1. In the first method, the gene of interest is isolated from the total genomic DNA of an organism. To isolate a gene, the genomic DNA is treated with a restriction endonuclease enzyme to cut it into many chunks. These pieces/fragments of DNA are then separated according to their length by electrophoresis. The separated DNA segments are finally used for cloning.
2. In the second method, the desired gene is synthesized using reverse transcription of the mRNA of the gene. The new DNA formed by this process is known as complementary DNA (cDNA).
3. In the third method, the preferred gene is produced by a programmed machine referred to as a DNA synthesizer or gene machine. The gene is thereby amplified by PCR and desired DNA (gene of interest) is referred to as transient or target DNA or donor DNA.

1.9 ISOLATION OF DNA VECTOR

The DNA, which is used for transferring the desired DNA (gene of interest) into a host cell or organism, is known as a vector. It is also called a cloning vehicle or carrier molecule. They are self-replicating in an appropriate

host cell. Vectors are of two kinds: plasmids (e.g., pBR322) and DNA viruses (e.g., lambda phages).

1.10 CONSTRUCTION OF RECOMBINANT DNA (RDNA)

Both the passenger and vector DNAs are separated with the same restriction endonucleases (ER) to produce complementary sticky ends. Self-ligation is prevented by using *alkaline phosphatase* (ALP). Both passenger and vector DNAs are now joined together using DNA ligase (Gupta, Sengupta, Prakash, and Tripathy, 2017). The vector is guaranteed to receive only one passenger DNA. Inserting the selected DNA (passenger DNA) into the cloning vector (e.g., plasmid) produces rDNA. The rDNA is also called Chimeric DNA. Chimera in Greek Mythology refers to a monster that has a lion's head, a goat's body, and a serpent's tail.

1.11 INTRODUCTION OF RDNA INTO HOST CELL

Introducing rDNA into a host cell is a significant step in genetic engineering. It is the efficiency of this process that determines success. This is accomplished by any of the methods discussed in subsections.

1.11.1 TRANSFORMATION

Direct transformation of DNA fragments in the medium by bacterial cells is called transformation. This method was first adopted in 1970 by Mandell and Higa (1970). The ability of bacterial cells to take DNA from the medium is known as competence.

In transformation, the alien DNA is injected into a bacterial cell (for example, E-COLI). The uptake of Foreign DNA by E-coli is carried out in ice-cold CaCl_2 (0–5°C) trailed by heat shock (37–45°C) for about 90 seconds.

1.11.2 TRANSFECTION

The direct intake of naked DNA from the culture medium by eukaryotic cells is termed as transfection (Neumann, Schaefer-Ridder, Wang, & Hofschneider, 1982). Transfection is similar to transformation in the case of bacteria. It occurs in plant cells and animal cells.

In this method, DNA is first dissolved in the phosphate buffer and Calcium chloride solution is added to it which leads to the formation of calcium phosphate precipitate. The precipitate is then added to the cells which lead to the adherence of the precipitate particles with the cell surface. The cells engulf the particles along with DNA by the process of phagocytosis. The DNA entering the cell is integrated with the cell's genome.

1.11.3 CONJUGATION

A naturally occurring microbial recombination also referred to as bacterial mating which occurs when two bacteria (one donor and one recipient) meet together, join by a cytoplasmic bridge or conjugation tube, and exchange the DNA (from donor to recipient). Within the recipient cell, the new DNA either integrates with the chromosome or remains free.

1.11.4 ELECTROPORATION

Electroporation works on the principle of high voltage electrical impulses. Electroporation is a technique that uses membrane permeability through the electric field. Neumann et al. reported in 1982, how alien DNA can be introduced into mouse cells using short pulses of high voltage electric field (Neumann et al., 1982). It causes the absorption of DNAs into protoplasts through the temporary permeability of the plasma membrane to macromolecules. Electric shocks generate pores in the membrane by damaging them. DNA diffuses through these membranes immediately after the electric field is applied. Transformation of *E. coli* cells by electroporation was finally published in 1988 (Carter & Shieh, 2015).

1.11.5 GENE TRANSFER THROUGH LIPOSOMES

Liposomes are circular lipids with an aqueous interior that can transport nucleic acids. The liposome-mediated gene transfer is referred to as Lipofection (Carter & Shieh, 2015). This technique was used as a carrier for the incorporation of nucleic acids into plant protoplasts. The liposome-treated pieces of DNA are encapsulated in them. These liposomes may then adhere

to cell membranes and merge with them to transfer DNA fragments. In this way, DNA penetrates the cell and then into the nucleus.

1.11.6 DIRECT TRANSFER OF DNA

1.11.6.1 PARTICLE BOMBARDMENT OR BIOLISTICS

Shooting of plant or animal cells by DNA-coated gold or tungsten particles for introducing DNAs into cells. It is also known as microprojectile bombardment. This method is employed for incorporating rDNA into plant cells, fungal cells, animal cells, and cell organelles such as mitochondria and chloroplast (O'Brien & Lummis, 2011). The instrument used to shoot the DNA into the cells is called a Gene gun or Microprojectile gun. Vector is not used in this method to incorporate rDNA into the host cells. The gene gun is used in place of Vector.

1.11.6.2 MICRO-INJECTION

It refers to the injection of DNAs or cell organelles directly into host cells using an injection method. This DNA is usually employed to inject the DNA directly into the animal cells, eggs, zygotes, and plant protoplasts. In this method, fertilized egg (Host cell) is transferred into a microscopic slide placed under the microscope. The host cell is then maintained in place using a suction pipette. One end of the sucking pipette is positioned on the surface of the cell and gentle suction is applied on its other end. The rDNA is sucked into a glass injection needle and is gently inserted into the zygote by viewing through the microscope. The rDNA is delivered into the zygote and the needle is drawn back carefully. In this way, the rDNA gets into the genome of the zygote.

1.12 SELECTION AND MULTIPLICATION OF RECOMBINANT HOST CELLS

Selection is a fundamental process in which, when the rDNA is inserted into a particular host cell, it becomes necessary to detect the cells that have received the recombinant or foreign DNA molecule. This process

is referred to as Screening or Selection. A Host cell containing rDNA is called recombinant or transformant. In this step, the transformed cells are separated from the non-transformed cells by using various methods such as antibiotic resistance, colony hybridization, and blotting tests, etc., using marker genes. The recombinant cells are mass cultured to test the purity of the products of the cloned genes.

1.13 EXPRESSION OF THE CLONED GENES

Finally, consideration should be given to ensure that the gene of interest is expressed as a functional protein. It is isolated and immunologically tested. The recombinant producing pure product (e.g., insulin) can readily be used in the future. The transformed host cells are also multiplied to produce enough copies (Figure 1.5).

1.14 APPLICATIONS OF GENETIC ENGINEERING

Manipulation of genetic constitution of organisms by inserting a gene of interest is called Genetic engineering. In genetic engineering, a novel gene can be incorporated into closely linked organisms as well as unrelated organisms. Through genetic engineering, many novel strains of micro-organisms, plants, and animals have been developed. These are very useful in agriculture, industries, pharmaceuticals, and environment.

1.14.1 TRANSGENIC ANIMALS

Transgenic animals are developed by manipulating their genetic makeup and introducing a new gene which is later expressed. These animals are utilized in the following ways:

- Transgenic animals are purposely designed to understand the control of genes and their impact on the normal functioning of the body and its developments. The best example in this regard is studying the biological role of insulin-like growth factor.
- The transgenic animals are developed to boost our understanding of result of genes which have role in development of diseases. Eventually, transgenic animals serve as model for human diseases.
- Transgenic animals are developed by introduction of a portion of DNA that encodes a product from the organism. Some of the

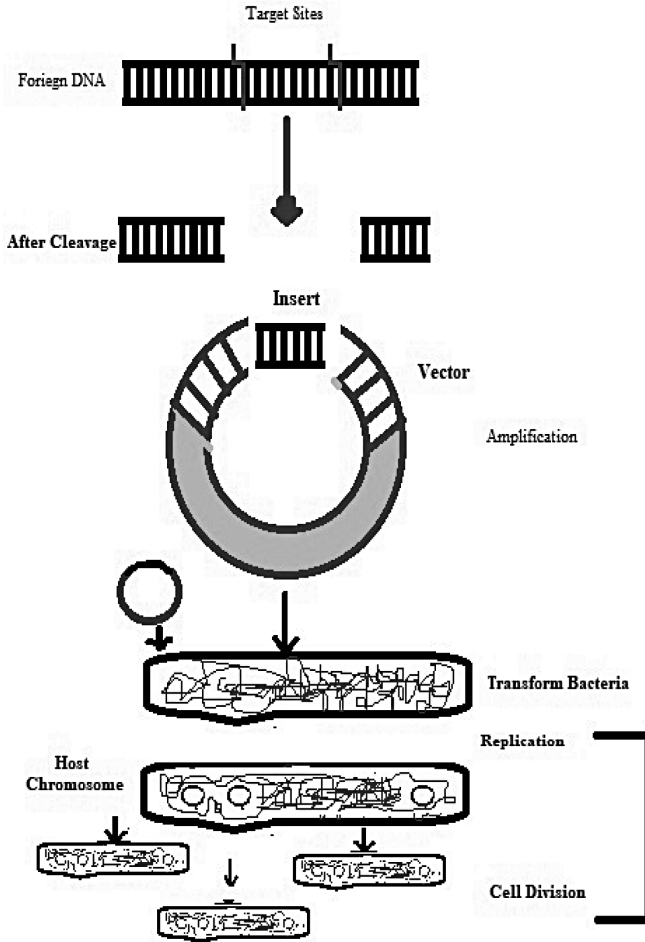


FIGURE 1.5 The process of genetic engineering.

useful biological compounds produced by this include a human protein namely alpha-1 antitrypsin used to treat emphysema. The first transgenic cow, Rosie, formed the human protein-rich milk; besides it possessed human alpha-lactalbumin, a nutritionally balanced product for babies. Transgenic cows with K-casein gene-insert produce milk rich in K-casein. This milk is likely for cheese making. Transgenic mice are also produced to test the efficacy and safety of vaccines like COVID-19 and HIV.

- Transgenic animals with high sensitivity to toxins are produced to observe and analyze the toxicity of drugs.
- Transgenic goats with tPA gene produce plasminogen activator in the milk. The tPA is used to dissolve blood clots.

1.14.2 TRANSGENIC PLANTS

The exercise of genetically modified (GM) plants has revolutionized the whole world and are very handy in the following ways:

- Genetic modification resulted in productions of better crops which are very resistant to abiotic stresses like frost, high temperature, drought, and high osmolarity, etc. (Davies, 2007).
- The use of synthetic pesticides has been declined as the crops are originally being GM for pest resistance.
- Damage to the crop after harvesting is also reduced.
- The nutrient content of soil is also preserved due to efficient mineral uptake by these crops.
- Food produced from GM crops has better dietary and nutritional value.
- Genetic alteration has been employed to generate need specific plants to deliver resources to industries like starch, fuel, pharmaceuticals, etc.

1.14.3 PRODUCTION OF PEST RESISTANT PLANTS

1.14.3.1 BT COTTON

The soil bacterium *Bacillus thuringiensis* transcribes crystal proteins known as *cry proteins*. These proteins are lethal to larvae of insects like Tobacco budworm, beetle worms and mosquitoes. The cry proteins are present in inactive form as protoxins and get transformed into active form when internalized by the organism, as the alkaline pH of gut solubilizes the toxin. The active toxin gets attached to the exterior of epithelial cells of midgut and generates pores. This results in enlargement and lysis of cells which ultimately causes the death of the Larva. These genes (cry genes) are isolated from the bacterium and integrated into numerous plants like tomato, cotton, corn, rice, soybean, etc. (Newell, 2000).

Below are the names of some of the cry genes encoding proteins against pests:

- Cry I Ac and cry II Ab manages cotton bollworms;
- Cry I Ab manages corn borer;
- Cry III Ab manages Colorado potato beetles.
- Cry III Bb manages corn rootworm.

1.14.3.2 DEFENSE AGAINST NEMATODES

Yield of tobacco plant is greatly affected by nematode namely *Meloidogyne incognita*. In order to prevent this. A special gene from the parasite is incorporated into the plant by means of *Agrobacterium* vector. The genes are incorporated in such a way that both sense and antisense RNA get formed. Being complementary to each other, they form double-stranded ribonucleic acid (RNA). As a result of this, specific RNA of nematode gets neutralized. This process is called RNA-interference. The whole process result nullifies the host and cannot assemble with a transgenic host which contributes in the host plant defense.

1.14.3.3 USE OF RDNA TECHNOLOGY IN THE MEDICAL FIELD

rDNA technology has paved the way in the production of highly efficient therapeutic drugs. Furthermore, therapeutics produced by recombination does not produce any harmful and unnecessary immunological response, which is very common in analogous products isolated from non-human resources. The current tally of approved recombinant therapeutics is 30. Out of these 30, 12 are already marketed in India.

1.14.3.4 HIMULIN – GENETICALLY ENGINEERED (GE) INSULIN

Himulin is genetically engineered (GE) form of insulin. Structurally human insulin contains two polypeptide chains as chain A and chain B, bonded by disulfide bridges.

Insulin is produced in an inactive form as prohormone and has to be processed before it attains complete functional structure. During its maturation, a polypeptide, namely C-peptide is scissored and maturation is attained. American company namely Eli-Lilly in 1983 synthesized two

DNA sequences responsible for producing chain A and B of functional insulin. They introduced this DNA in *E. coli* plasmid thereby producing insulin. Polypeptide chains produced were harvested and linked by the introduction of disulfide bonds.

1.14.3.5 GENE THERAPY

With the advancement of genetic engineering, it is now possible to treat certain genetic diseases. The method relies on the introduction of genes in cells and tissues of that individual. The defective gene is primed and new normal gene is delivered into the embryo or individual. Eventually the normal gene replaces the faulty mutant allele. The new genes are introduced in individual, and the process is mediated by special transporters called vectors. Viruses which infect the host and introduce their own genetic material there are designed in such a way that they act as vectors. The first documented gene therapy was done in the 1990s to a four-year-old girl, who had a deficiency of adenosine deaminase (ADA). Since ADA deficit can be corrected by bone marrow transplantation in certain children but it is not fully remedial. Lymphocytes are developed in a functional ADA. cDNA is incorporated into lymphocytes. These lymphocytes are then transferred in patient's body. A permanent cure is only possible if the same gene is incorporated in the patient's bone marrow cells in the embryonic stage.

1.14.3.6 MOLECULAR DIAGNOSIS

rDNA techniques like PCR (polymerase chain reaction) are useful in the early diagnosis of disorders. The cloned genes are also employed as 'probes' to spot the existence of complementary DNA strand. Eventually, a probe is a single-stranded DNA that is labeled with a radioactive tag and is used to discover its complementary DNA by hybridization. Afterwards, recognition of radioactivity by autoradiography is done. Existence of a normal or mutant gene can be identified by this method. Thus, PCR is a very powerful tool in the detection of genetic disorders besides other diseases like HIV. During the current global crises of COVID-19, PCR has served one the best and only technique to identify the presence of the virus.

1.15 SAFETY CONCERNS REGARDING GENETIC ENGINEERING

Genetically modified organisms (GMO) are primarily developed by introducing a minute segment of DNA from a “donor” into a “recipient” organism. The genome of the new organism is thus most likely that of the recipient organism. Consequently, the new organism contains fraction of recipient thus accessing the properties of recipient may provide as initial insight and assessment of properties of the new organism. Thus, a framework for safety assessment mainly depends on a range of differences in the genetic makeup of recipient and modified organism.

KEYWORDS

- **bacterial artificial chromosomes**
- **deoxyribonucleic acid**
- ***Escherichia coli***
- **mammalian artificial chromosomes**
- **P1-derived artificial chromosomes**
- **yeast artificial chromosome**

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Introduction of Recombinant DNA into Host Cells

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Genetically Engineered Microorganisms

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