Unified Patent Court
Einheitliches Patentgericht
Juridiction unifiée du brevet

The Hague - Local Division
UPC_CFI_187/2024
UPC_CFI_507/2024

Decision
of the Court of First Instance of the Unified Patent Court
delivered on 18/11/2025
regarding EP1910572 and EP2500439

CLAIMANT/S

1)	**Advanced Cell Diagnostics, Inc.** (Claimant) - 7077 Gateway Blvd., - CA 94560, - Newark, - US	Represented by Judith Krens, Christopher Sharp, Kristina Cornish and Nicolas Bitsch

DEFENDANT/S

1)	**Molecular Instruments, Inc.** (Defendant) - 5015 Eagle Rock Blvd., Ste 301 CA 90041, - Los Angeles, - US	Represented by Marianne Schaffner, Matthew Spencer, James Legg, Anne Marie Verschuur and Celine Bey

PATENTS AT ISSUE

Patent no.	*Proprietor/s*
EP1910572	Advanced Cell Diagnostics, Inc.
EP2500439	Advanced Cell Diagnostics, Inc.

DECIDING JUDGES

The panel of the LD The Hague, comprising:

Presiding judge	Edger Brinkman
Legally qualified judge	Alima Zana
Judge-rapporteur	Margot Kokke
Technically qualified judge	Michael Alt

LANGUAGE OF PROCEEDINGS: English
ORAL HEARING: 2 October 2025

I. SUMMARY OF FACTS AND PROCEDURE

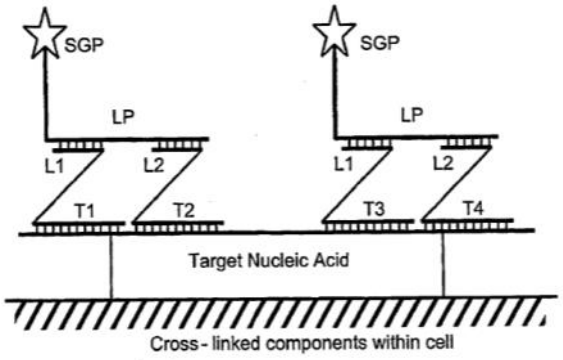
The Claimant and the patents

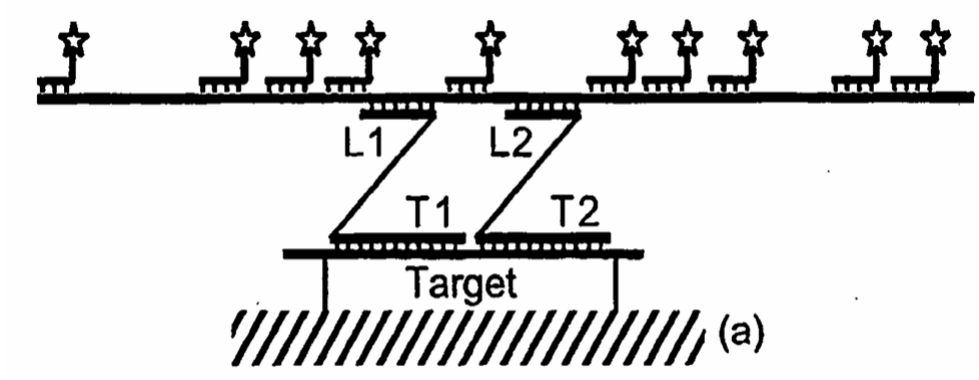
1. The Claimant is a company based in California, US, and is part of the globally operating Bio-Tech group. It is in the business of developing assays and other platforms used in the analysis of nucleic acid molecules, specifically also ribonucleic acid ("**RNA**") molecules. It has developed inter alia, an assay consisting of a multiplex fluorescent and chromogenic *in situ* hybridization ("**ISH**"), capable of detecting and quantifying single molecules of RNA *in situ*. It refers to this technology as RNAscope technology.

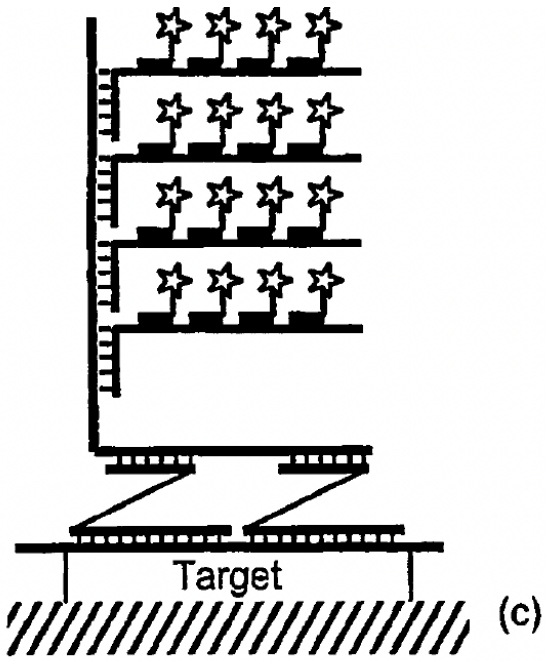
2. Claimant is the registered proprietor of the patents at issue, European patent 2 500 439 B2 ("**EP439**") and European Patent 1,910,572 B1 ("**EP572**") (collectively, the "**patents**"). The patents relate to RNA-scope technology.

3. EP572 was filed on 19 June 2006 as an international application that was published on 4 January 2007 as WO 2007/001986 A2 ("**WO986**"), claiming priority to a US provisional application filed on 20 June 2005. EP572 was granted on 30 December 2015, entitled "*Methods of detecting nucleic acids in individual cells and of identifying rare cells from large heterogeneous cell populations*". This patent was validated on grant in DE, FR, NL, DK, UK, IT, CH/LI and ES. No opposition was filed against the grant of EP572.

4. The patent specification of EP572 contains twelve method claims. All subclaims depend on independent method claim 1 which is directed at the *in situ* detection of one or more nucleic acid targets within an individual cell, starting with fixing and permeabilising the cell. This will be discussed in more detail below. Figures 4, 8a and 8c of EP572 are reproduced below respectively.







5. The description of EP572 contains inter alia the following:

BACKGROUND OF THE INVENTION

(...)**[0007] I**n situ hybridization (ISH) technology is an established method of localizing and detecting specific mRNA sequences in morphologically preserved tissue sections or cell preparations (Hicks et al., 2004). (…) Detection is carried out using nucleic acid probes that are complementary to and hybridize with specific nucleotide sequences within cells and tissues. The sensitivity of the technique is such that threshold levels of detection are in the range of 10-20 copies of mRNA per cell.

[0008] However, ISH technology faces a number of technical challenges that limit its wide use. First of all, cells immobilized on solid surface exhibit poor hybridization kinetics. Secondly, assay optimization is generally required for a target mRNA in probe selection, labeling, and detection, for each tissue section in fixation and permeabilization, and in hybridization and washing. In addition, various experiments need to be performed to control for the specificity of the probe, for tissue mRNA quality, and for the hybridization efficacy of the experimental procedure. In addition to technical issues, current ISH technology has relatively low performance standards in term of its detection sensitivity and reproducibility. The false positive rate is still high unless the relevant cells are reexamined manually using their morphology, which is time and labor-intensive. Current ISH technology also does not have the capability to quantitatively determine the mRNA expression level or to simultaneously measure the expression of multiple target mRNA within cells, which may provide clinical valuable information such as increased detection sensitivity and specificity, and the identification of primary tumor type, source and stage.

[0009] There are four main types of probes that are typically used in performing in situ hybridization within cells: oligonucleotide probes (usually 20-40 bases in length), single-stranded DNA probes (200-500 bases in length), double stranded DNA probes, or RNA probes (200-5000 bases in length). RNA probes are currently the most widely used probes for in situ hybridization Furthermore, with direct labeling methods, there is no good way to control for potential cross-hybridization with non-specific sequences in cells. Branched DNA (bDNA) in situ hybridization is an indirect labeling method for detecting mRNA in single cells (Player et al, 2001; US 2002, 0172950). Branched DNA ISH has also been evaluated for detection of nucleic acids sequences in tissue specimens (Kenny et al, 2002). This method uses a series of oligonucleotide probes that have one portion hybridizing to the specific mRNA of interest and another portion hybridizing to the bDNA for signal amplification and detection. bDNA ISH has the advantage of using unlabeled oligonucleotide probes for detecting every mRNA of interest and the signal amplification and detection are generic components in the assay. However, the gene specific probes in the bDNA ISH need to be theoretically screened against

possible non-specific hybridization interactions with other mRNA sequences in the cells. The nonspecific hybridization of the oligonucleotide probes in bDNA ISH can become a serious problem when multiple of those probes have to be used for the detection of low abundance mRNAs. Similarly, although use of bDNA ISH to detect or quantitate multiple mRNAs is desirable, such nonspecific hybridization of the oligonucleotide probes is a potential problem. **[0010]** The present invention overcomes the above noted difficulties and provides methods for detecting nucleic acids in and for identifying individual cells. A complete understanding of the invention will be obtained upon review of the following.

(…)

BRIEF DESCIPTIONS OF THE DRAWINGS

[0069] (….) **Figure 4** schematically illustrates an indirect labeling capture probe design approach that utilizes a pair of independent capture probes to enhance the specificity of the label probe capture to the target nucleic acid. (…)

Figure 8 Panels A-D schematically illustrate different structures of exemplary amplifiers.

(…)

DEFINITIONS

(…)

[0078] Two polynucleotides "hybridize" when they associate to forma stable duplex, e.g., under relevant assay conditions. Nucleic acids hybridize due to a variety of well characterized physico-chemical forces, such as hydrogen bonding, solvent exclusion, base stacking and the like.(…)

[0079] A first polynucleotide "capable of hybridizing" to a second polynucleotide contains a first polynucleotide sequence that is complementary to a second polynucleotide sequence in the second polynucleotide. The first and second polynucleotides are able to form a stable duplex, e.g., under relevant assay conditions.

(…)

[0081] The term "complementary" refers to a polynucleotide that forms a stable duplex with its "complement," e.g., under relevant assay conditions. Typically, two polynucleotide sequences that are complementary to each other have mismatches at less than about 20% of the bases, at less than about 10% of the bases, preferably at less than about 5% of the bases, and more preferably have no mismatches.

[0082] A "label" is a moiety that facilitates detection of a molecule. (…)

[0083] The term "label probe" refers to an entity that binds to a target molecule, directly or indirectly, and enables the target to be detected, e.g., by a readout instrument. A label probe (or "LP") is typically a single-stranded polynucleotide that comprises at least one label which directly or indirectly provides a detectable signal. The label can be covalently attached to the polynucleotide, or the polynucleotide can be configured to bind to the label (e.g., a biotinylated polynucleotide can bind a streptavidin-associated label). The label probe can, for example, hybridize directly to a target nucleic acid, or it can hybridize to a nucleic acid that is in turn hybridized to the target nucleic acid or to one or more other nucleic acids that are hybridized to the nucleic acid. Thus, the label probe can comprise a polynucleotide sequence that is complementary to a polynucleotide sequence of the target nucleic acid, or it can comprise at least one polynucleotide sequence that is complementary to a polynucleotide sequence in a capture probe, amplifier, or the like.

[0084] A "capture probe" is a polynucleotide that is capable of hybridizing to a target nucleic acid and capturing

a label probe to that target nucleic acid. The capture probe can hybridize directly to the label probe, or it can hybridize to one or more nucleic acids that in turn hybridize to the label probe; for example, the capture probe can hybridize to an amplifier or a preamplifier. The capture probe thus includes a first polynucleotide sequence that is complementary to a polynucleotide sequence of the target nucleic acid and a second polynucleotide sequence that is complementary to a polynucleotide sequence of the label probe, amplifier, preamplifier, or the like. The capture probe is preferably single-stranded.

[0085] An "amplifier" is a molecule, typically a polynucleotide, that is capable of hybridizing to multiple label probes. Typically, the amplifier hybridizes to multiple identical label probes. The amplifier also hybridizes to at least one capture probe or nucleic acid bound to a capture probe.

(…)
METHODS OF DETECTING NUCLEIC ACIDS AND (meant is: IN, the Court) CELLS
Multiplex detection of nucleic acids
[0095] As noted, the invention generally relates to multiplex nucleic acid assays in single cells. Thus, one general class of embodiments includes methods of detecting two or more nucleic acid targets in an individual cell. In the methods, a sample comprising the cell is provided. The cell comprises, or is suspected of comprising, a first nucleic acid target and a second nucleic acid target. A first label probe comprising a first label and a second label probe comprising a second label, wherein a first signal from the first label is distinguishable from a second signal from the second label, are provided. At least a first capture probe and at least a second capture probe are also provided.
(…)
[0102] In methods in which two or more first capture probes and/or two or more second capture probes are employed, the capture probes preferably hybridize to nonoverlapping polynucleotide sequences in their respective nucleic acid target. The capture probes can, but need not, cover a contiguous region of the nucleic acid target. Blocking probes, polynucleotides which hybridize to regions of the nucleic acid target not occupied by capture probes, are optionally provided and hybridized to the target. For a given nucleic acid target, the corresponding capture probes and blocking probes are preferably complementary to physically distinct, nonoverlapping sequences in the nucleic acid target, which nonoverlapping sequences are preferably, but not necessarily, contiguous. Having the capture probes and optional blocking probes be contiguous with each other can in some embodiments enhance hybridization strength, remove secondary structure, and ensure more consistent and reproducible signal.
(…)
[0117] The various capture and hybridization steps can be performed simultaneously or sequentially, in essentially any convenient order. Preferably, a given hybridization step is accomplished for all of the nucleic acid targets at the same time. For example, all the capture probes (first, second, etc.) can be added to the cell at once and permitted to hybridize to their corresponding targets, the cell can be washed, amplifiers (first, second, etc.) can be hybridized to the corresponding capture probes, the cell can be washed, the label probes (first, second, etc.) can be hybridized to the corresponding amplifiers, and the cell can then be washed again prior to detection of the labels. As another example, the capture probes can be hybridized to the targets, the cell can be washed, amplifiers and label probes can be added together and hybridized, and the cell can then be washed prior to detection. (…)
(..)
IMPLEMENTATION, APPLICATION, AND ADVANTAGES
[0185] Various aspects of the invention are described in additional detail below. Exemplary embodiments and applications are also described.
[0186] The new technology (methods, compositions, systems, and kits), QMAGEX (Quantitative Multiplex Analysis of Gene Expression in Single Cell), disclosed herein is capable of detection and quantification of multiple nucleic acids within individual cells. The technology is significantly different from existing ISH technology in several aspects, although they both can measure mRNA expression in individual cells. First, cells preferably remain in suspension status during all or at least most of the assay steps in the assays of the present invention, which greatly improves assay hybridization kinetics, resulting in better reproducibility and shorter assay time. Second, the instant technology has the capability for analyzing the expression of multiple mRNA transcripts within cells simultaneously and quantitatively. This is highly desirable, since, for example, detection of multiple tumor marker genes could greatly improve the accuracy of CTC identification (Mocellin et al., 2004) and greatly reduce the false positive rate. Quantitative analysis of gene expression level could not only further aid in discriminating the CTC from other types of cells but also could help in distinguishing the type and source of primary tumors as well as the stages of tumor progression. Third, the instant technology enables the use of a flow cytometer as the base for detection, which, compared with microscope-based detection instruments, offers higher throughput. In addition, the flow cytometer is capable of sorting out cells, e.g., tumor cells, for further study. Subsequent to the detection and quantification of mRNA expression, isolation of the CTC or other cells may be advantageous for further identity confirmation or for additional cytological and molecular analysis.

Fourth, the instant technology has vastly improved detection sensitivity and reproducibility, and is capable of single copy gene detection and quantification. In addition, the instant technology uses a standard, generic set of probe labeling and detection technology (e.g., the same set of preamplifiers, amplifiers, and label probes can be used to detect multiple dif-ferent sets of nucleic acid targets, requiring only synthesis of a new set of capture probes for each new set of nucleic acid targets), and optionally uses standardized procedures for cell fixation and permeation and for hybridization and washing. Furthermore, the technology can include built-in internal controls for assay specificity and efficiency.

[0187] The instant technology can be used not only for the detection and enumeration of rare CTC in blood samples or other body fluids, but also for any type of rare cell identification and enumeration events. (…)

Probe selection and design

[0204] The assays of the invention employ two types of approaches in probe design to link the target nucleic acids in cells to signal generating particles: "direct labeling" and "indirect labeling". In the direct labeling approach, the target molecule hybridizes to or captures one or more label probes (LP) directly. The LPs contain the signal-generating particles (SGP), as shown in Figure 2. (…) In order to ensure hybridization specificity, the label probe is preferably stringently selected to ensure that it does not cross- hybridize with nonspecific nucleic acid sequences.

(…)

[0207] In a further indirect capture embodiment shown in Figure 4, two adjacent capture probes are incorporated in a probe set targeting a gene of interest. T1 and T2 are designed to be complementary to two unique and adjacent sections on the target nucleic acid. L1 and L2, which can be different or the same, are complementary to two adjacent sections on the label probe. Their binding sections, T, L or both, are designed so that the linkage between the label probe and the target is unstable and tends to fall off at hybridization temperature when only one of the capture probes is in place. Such a design should enable exceptional specificity because the signal-generating label probe can only be attached to the target gene of interest when two independent capture probes both recognize the target and bind to the adjacent sequences or in very close proximity of the target gene. (…)

6. EP439 is a divisional of EP572. This patent was granted on 13 August 2014 for '*Kits and products for detecting nucleic acids in individual cells and of identifying rare cells from large heterogeneous cell popula*tions' and was validated on grant in DE, FR, NL, DK, UK, IT, ES and CH/LI. As the result of opposition proceedings, EP493 was maintained in an amended (B2) form that was published on 16 August 2017. EP493 as it is now valid has eight product claims. Claim 1 pertains to a kit for detecting a nucleic acid in an individual cell. Claim 2 depends on claim 1 and also relates to a kit. Claim 3 is directed at a sample of fixed and permeabilized cells. Claims 4-8 depend on claim 3.

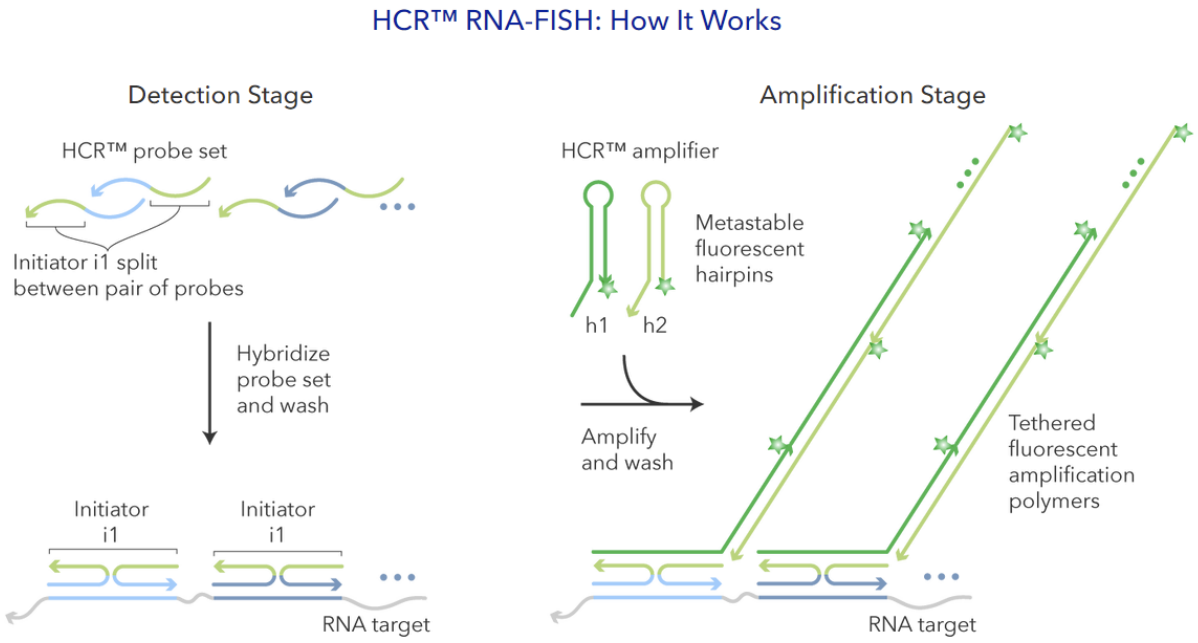
7. The patent specification of EP439 contains the same figures as EP572.

<u>The Defendant and its products</u>

8. The Defendant is a US company. The Defendant is a biotech startup that develops and commercializes molecular technologies for detecting DNA, RNA and proteins, including HCR RNA fluorescence in situ hybridization ("**FISH**") technology.

9. The Defendant's FISH products include a kit of probes and related components that are intended to be used in accordance with a specific protocol of detecting one or more nucleic acid targets within an individual cell using ISH techniques. The kits of probes are referred to as HCR 3.0 / HCR RNA-FISH products (the "**HCR Products**"). The HCR Products detect one or more nucleic acids in a particular cell in accordance with the Defendant's HCR RNA-FISH protocols

(the "**HCR Protocols**"), as referred to on Defendant's websites for the purpose of preparation of sample(s) of fixed and permeabilized cells. The following overview taken from MI's websites illustrates how the detection of an RNA target with the HCR Products works.



10. Defendant offers the HCR Products for sale on the websites https://www.molecularinstruments.com/ and https://www.hcrimaging.com/ (the "**MI Websites**"). The MI Websites do not contain geographical restrictions for sales, in particular the offering and sale of the HCR Products to customers located outside the United States of America, including customers residing within UPCA-territory, is not limited or excluded. The Claimant successfully commissioned the purchase of HCR Products from the website by an intermediary at the University Hospital in Heidelberg, Germany, via personnel working at the Center for Integrative Infectious Disease Research (CIID) at the University Hospital. Two different purchases were made via the website and were delivered to Heidelberg University Hospital, Germany, in October 2023 and January 2024.

Procedure

11. On 22 April 2024, Claimant filed a statement of claim ("SoC") to start this infringement action. Together with its statement of defence ("SoD"), Defendant filed a counterclaim for revocation, in response to which the Claimant submitted a conditional application to amend the patents filing two auxiliary requests for each patent. Further written submissions were exchanged as foreseen by the rules of procedure ("RoP"). For further details and interim applications, reference is made to the CMS.

12. An interim conference was held on 2 July 2025. Inter alia the following decisions were taken, and instructions were given there:

    I. The value of the infringement proceeding/action is set at **EUR 5,000,000.-.**
    II. The value of the counterclaim proceedings/action is set at **EUR 5,000,000.-.**
    III. The parties agree on the product description from the UK proceedings between the same parties (exhibit D030);

IV. The parties agree on the Statement of agreed common general knowledge from the UK proceedings between the same parties (exhibit D038);
V. (…) Claimant's R.190 application (App_26938/2025) is withdrawn (…);
VI. The Defendant no longer relies upon its added matter arguments that apply only to the additional integers present in claims 7 and 9 of EP572 as filed (paragraphs 434-437 and 442-444 of its counterclaim for revocation);
(…)
IX. In case the parties cannot reach an agreement on legal costs, the parties will submit an estimate of the legal costs that they seek to recover two weeks before the oral hearing, which estimate can be updated 24 hours before the oral hearing. In case an agreement is reached on the costs, the court is also to be informed.
(…)

13. The oral hearing was held on 2 October 2025.

Parallel proceedings

14. In proceedings between the same parties concerning infringement of the UK designations of the patents with the same products before the High Court of England and Wales (the "High Court"), the patents were considered invalid for obviousness over Collins with Kern (see below) by judgment published on 23 April 2024. Had the patents been found to be valid, EP572 but not EP439 would have been infringed with the HCR Product.

II. REMEDIES SOUGHT AND SUBMISSIONS

15. Asserting that the Defendant infringes method claims 1 and 11-16 of EP572 and kits and samples of claims 1-8 of EP439 literally or by equivalence, directly or indirectly, with its HCR Products, the Claimant requests – as the Court understands; separate requests are not included in the SoC – that the Court, in summary, prohibits Defendant from infringing the patents in the contracting member states where the patents are in effect, together with additional remedies (deliver up and/or destruction of infringing products, recall, publication of a declaration of infringement), damages and legal costs.

16. Defendant requests that the Court dismiss the infringement action and order the Claimant to pay the legal costs and other expenses of the proceedings. Thereto it submits inter alia that the HCR Products do not have non-overlapping regions as required by features 1.h of EP572 and feature 1.f of EP439 because there is an overlap of 1-4 nucleotides in the regions of the label probe to which the L sections of the capture probes are complementary. In the counterclaim action, Defendant requests the Court to revoke the patents in their entirety because the claimed subject matter is neither novel nor inventive over the prior art and/or because the patents contain unpermitted added matter and suffer from insufficiency of disclosure. It also requests the Court to order the Claimant to bear costs and other expenses of the counterclaim proceedings.

III. III.GROUNDS FOR THE DECISION

III.A – JURISDICTION, COMPETENCE AND SUMMARY

International jurisdiction and competence

17. The Defendant did not file a preliminary objection within the timeframe of R.19.1 RoP. Pursuant to R.19.7, the Defendant is therefore considered to submit to the jurisdiction of the UPC and to the competence of the LD The Hague. In view of the allegedly infringing acts (the offering of the HCR Products on the MI website which is also directed at UPC territory, including the Netherlands, and the effected sales to customers in Germany, see 10. above), the Court also sees no reason to deny jurisdiction ex officio. International jurisdiction of the UPC follows from Art. 7(2) BR and competence of the LD The Hague from Art. 33.1(a).

Summary

18. It is not in dispute that the Claimant is the owner of the patents and has standing to sue. The Court finds that independent claims 1 of the patens and claim 3 of EP439 are valid but not infringed. The reasons for the findings are discussed in part III.C (for validity) and III.D (for infringement) below. First, the Court will address the teaching of the patent, the skilled person and the interpretation of the claims in III.B. In part III.E the consequences of the outcome for the decision will be addressed, as well as the costs.

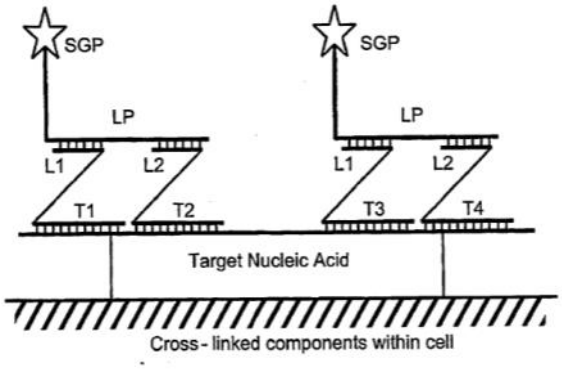
III.B –TEACHING OF THE PATENTS, SKILLED PERSON AND CLAIM CONSTRUCTION

The patents

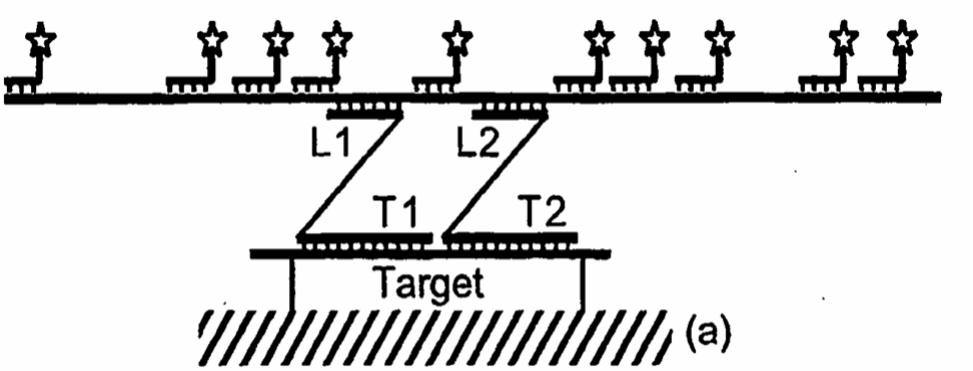
19. The patents aim to provide a method, a sample and a kit to detect rare nucleic acid targets in cells by hybridization techniques (“in situ hybridization”, “ISH”) with very high specificity, for instance in circulating tumour cells (“CTC”) (EP572 [0001]-[0010], EP439 [0001]-[0011]). Originating from the same application (WO986), the descriptions of the two patent specifications have considerable overlap but are not identical. The descriptions were evidently adapted during prosecution. When reference is made to paragraphs of the description, the description of EP572 is meant unless indicated otherwise.

20. The disclosed assays make use of branched DNA (“bDNA”) components as probes and amplifiers. At the priority date, it was common practice to use bDNA for this purpose in assays. The target nucleic acid is detected by a signal produced via the label of a label probe (“**LP**”). Claim 1 of EP572 covers three alternative embodiments, all of which are characterized in that the label probe does not bind directly to the target. Separate capture (or target) probes bind directly to the nucleic acid target. In the various embodiments, described in more detail below, the label probe either binds to two capture probes, to an amplifier that then binds to two capture probes or to an amplifier that binds to a pre-amplifier that in turn binds to the two capture probes.

21. According to the first claimed embodiment, shown in Fig. 4 reproduced below, two capture probes are used that link the target to the label probes. Each of the capture probes has a region binding to the target (T1 and T2 for a first target sequence or T3 and T4 for a second capture probe that binds to a second target sequence) and a region binding to the label probe (L1 and L2).

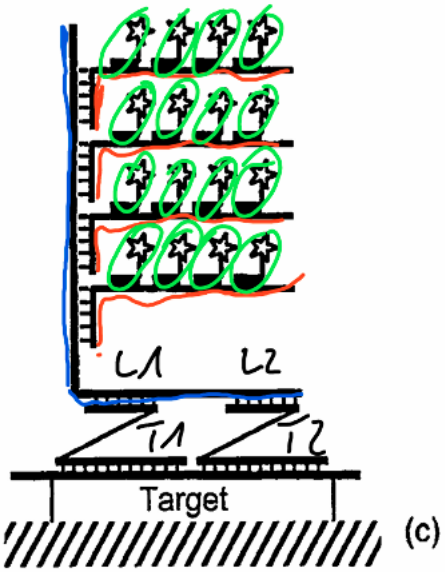


22. According to the second embodiment the capture probes and the label probes bind to an amplifier probe, i.e. the amplifier is sandwiched between the label probe and the capture probes which also means that the capture probes and the label probes do not bind directly. This is illustrated in Fig. 8a [of the patents]:



The amplifier is the long horizontal line to which the two capture probes bind via the L1 and L2 regions. To the amplifier the label probes bind, in this case 10 label probes identified by the stars, i.e. much more than in case of the first embodiment.

23. According to the third embodiment the capture probes bind to a pre-amplifier to which the amplifier binds to which the label probes bind, i.e. the amplifier and the pre-amplifier are sandwiched between the label probe and the capture probes which also mean that the capture probes and the label probes do not bind directly. This is illustrated in Fig. 8c (with colouring added by the Court):



24. The pre-amplifier is the long L-shaped line marked in blue to which the two capture probes bind via the L1 and L2 regions. To the pre-amplifier the amplifiers (marked in orange) bind and to the amplifier the label probes (marked in green) bind, in this case 16 label probes, i.e. much more than in case of the first and second embodiment.

25. The required double binding of one label probe (or of a (pre-)amplifier) to two capture probes, increasing specificity and decreasing background noise (thus filtering out undesired binding of single capture probes to other nucleotide sequences present in the samples), is also referred to as a cruciform structure in relevant scientific literature and by the parties. In the second and third claimed embodiments, with the (pre-)amplifiers, the signal is also increased. Furthermore, the complementary binding regions of T1 and T2 (or T3 and T4) to the target and of L1 and L2 to the label probes (or to (pre-)amplifiers), are said to be non-overlapping.

26. The patents describe several (capture and hybridisation) steps leading to the detection of one or more targets *in situ*. The steps include providing a sample, fixing and permeabilising a cell, hybridisation of the capture probes to the target, washing, hybridisation of the label probes to the capture probes, washing, and detection (see [0117] and claim 1 of EP572). The detection of two or more targets in an individual cell with one assay is referred to as multiplexing and the assays as multiplex nucleic acid assays. The claims of the patents are not limited to multiplexing.

27. All three embodiments are claimed (as alternatives) in the method of claim 1 of EP572, which reads as follows, divided into features:

FEATURE	EP572 - CLAIM 1
1(a)	A method of detecting one or more nucleic acid targets within an individual cell, the method comprising
1(b)	providing a sample comprising the cell, which cell comprises or is suspected of comprising one or more nucleic acid targets;
1(c)	fixing and permeabilising the cell;
1(d)	for each nucleic acid target, providing *(one of more from d) of)*:
1(d) (i)	one or more label probes, wherein each label probe comprises one or more labels,
1(d) (ii)	one or more label probes, and one or more amplifiers, wherein each label probe comprises one or more labels, and wherein each amplifier is capable of hybridizing to one or more label probes, or
1(d) (iii)	one or more label probes, one or more amplifiers, and one or more preamplifiers, wherein each label probe comprises one or more labels, wherein each amplifier is capable of hybridizing to one or more label probes, and wherein each preamplifier is capable of hybridizing to one or more amplifiers;
1(e)	for each nucleic acid target, providing two or more different capture probes,
1(f)	wherein each of the two or more capture probes comprises a section T complementary to a section on the nucleic acid target and a section L complementary to a section on the label probe, or on an amplifier, or on a preamplifier, and

1(g)	wherein the T sections are complementary to nonoverlapping regions of the nucleic acid target,
1(h)	and the L sections are complementary to nonoverlapping regions of the label probe, the amplifier, or the preamplifier;
1(i)	hybridising, in the cell, the two or more capture probes to a single copy of the nucleic acid target, when present in the cell;
1(j)	capturing the label probe to the two or more capture probes, thereby capturing the label probe to the nucleic acid target, (*by one of more of feature k*):
1(k) (i)	by simultaneously hybridising at least two different capture probes to a single copy of the label probe,
1(k) (ii)	or by simultaneously hybridizing at least two different capture probes to a single copy of the amplifier and hybridizing the label probes to the amplifier,
1(k) (iii)	or by simultaneously hybridizing at least two different capture probes to a single copy of the preamplifier and hybridizing the one or more amplifiers to the preamplifier and the one or more label probes to each of the one or more amplifiers; and
1(l)	detecting a signal from the label.

Features 1d(i) and 1k(i) correspond to the first embodiment, features 1d(ii) and 1k(ii) refer to the second embodiment and in features 1d(iii) and 1k(iii) the third embodiment described above is claimed.

28. Independent product claims 1 and 3 of EP439 also cover the three embodiments described above. Divided into features, these claims are:

FEATURE	EP439 - CLAIM 1
1(a)	A kit for detecting a nucleic acid in an individual cell comprising, packaged in one or more containers:
1(b)	at least one reagent for permeabilising cells;
1(c)	at least one capture probe set comprising two or more capture probes capable of hybridizing to a target nucleic acid sequence; and (*one or more from d*)

1(d) (i)	a label probe comprising a label, wherein the label probe is capable of hybridizing to said set of two or more capture probes, or
1(d) (ii)	a label probe comprising a label, and an amplifier hybridized to the label probe and capable of hybridizing to said set of two or more capture probes, or
1(d) (iii)	a label probe comprising a label, an amplifier hybridized to the label probe, and a preamplifier hybridized to the amplifier and capable or hybridizing to said set or two or more capture probes,
1(e)	wherein each said capture probe comprises a T section which is complementary to a region of said target nucleic acid sequence and an L section which is complementary to a region of said (i) label probe, (ii) amplifier or (iii) preamplifier;
1(f)	wherein the T sections of the two or more capture probes in the capture probe set are complementary to the non-overlapping regions of the target nucleic acid sequence, and the L sections of two or more capture probes in the capture probe set are complementary to the non-overlapping regions of said (i) label probe, (ii) amplifier, or (iii) preamplifier.

FEATURE	EP'4~~3~~9 - CLAIM 3
3(a)	A sample of fixed and permeabilized cells, comprising:
3(b)(i)	at least one fixed and permeabilised cell containing a target nucleic acid;
3(b)(ii)	at least one capture probe set comprising two or more capture probes hybridised to said target nucleic acid *(and one or more of):* and
3(c)(i)	a label probe hybridized to said set of two or more capture probes, or
3(c)(ii)	a label probe, and an amplifier hybridized to the label probe and capable of hybridizing to said set of two or more capture probes, or
3(c)(iii)	a label probe, and an amplifier hybridized to the label, and a preamplifier hybridized to the amplifier and capable of hybridizing to said set of two or more capture probes,
3(d)	wherein each said capture probe comprises a T section which is complementary to a region of said target nucleic acid and an L section which is complementary to a region of said (i) label probe, (ii) amplifier, or (iii) preamplifier;
3(e)	wherein the T sections of two or more capture probes in the capture probe set are complementary to non-overlapping regions of the target nucleic acid and the L sections of two or more capture probes in the set are complementary to non-overlapping regions of said (i) label probe, (ii) amplifier, or (iii) preamplifier.

Claim construction

29. The parties disagree on the interpretation of certain features of claim 1 of EP572 and of corresponding features of claims 1 and 3 of EP439. The Court of Appeal of the UPC ("CoA") has

set out the following principles regarding interpretation of a patent claim according to Art. 69 EPC.[1]

> The patent claim is not only the starting point, but the decisive basis for determining the protective scope of a European patent. The interpretation of a patent claim does not depend solely on the strict, literal meaning of the wording used. Rather, the description and the drawings must always be used as explanatory aids for the interpretation of the patent claim and not only to resolve any ambiguities in the patent claim. However, this does not mean that the patent claim merely serves as a guideline and that its subject-matter also extends to what, after examination of the description and drawings, appears to be the subject-matter for which the patent proprietor seeks protection.

The CoA also clarified (i) that the principles for interpreting a patent claim apply equally to the assessment of the infringement and to the validity of a European patent, (ii) that a patent must be interpreted from the point of view of the average person skilled in the art (the "skilled person") and (iii) that the aim of applying these principles is to combine adequate protection for the patent proprietor with sufficient legal certainty for third parties.

30. In this case the skilled person is assumed to be an experienced practitioner of nucleic acid detection techniques including both *in situ* and *in vitro* detection. The common general knowledge ("CGK") that the skilled person possesses is evidenced by (at least) what was agreed thereon in the UK proceedings, which was submitted in this action. This is not in dispute. The Defendant asserts that the CGK of the skilled person is broader than what was agreed in the UK. This is disputed.

31. Hereafter some relevant features of which the interpretation is in dispute or not entirely clear, are clarified. The Court will focus on independent claim 1 of EP572 but the interpretation also applies to corresponding features of subclaims and the claims of EP439.

    Feature 1(f): "*wherein each of the two or more capture probes comprises a section T complementary to a section on the nucleic acid target and a section L complementary to a section on the label probe*"

32. Functionally the label probe carries at least one label which enables the target to be detected as specified in [0083] of the description of EP572 (which corresponds to [0075] of EP438). The Claimant asserts that the interaction between the capture probe and the label probe can be either by direct hybridization or indirectly, via the hybridization of the capture probe to one or more nucleic acids that in turn hybridize to the label probe, as long as the function is achieved. This follows from [0084] of the description of EP572 ([0076] of EP428)

33. This interpretation is not in compliance with the clear wording of feature 1(f). The specific requirement of complementarity of the sequences limits the claim to a direct hybridization of the (T section of the) capture probe to the label probe. Only direct hybridisation therefore falls within the scope of the claim, as advocated by the Defendant.

    Feature 1(h): "*and the L sections are complementary to <u>nonoverlapping regions</u> of the label probe (…)*"

[1] Order CoA UPC, NanoString Technologies -v- 10x Genomics, UPC_CoA_335/2023, App_576355/2023 of 26 February 2024, as rectified by the order of 11 March 2024, headnote 2 and paragraph 5.d) aa) of the grounds. See also G1/24, Enlarged Board of Appeal EPO.

34. Regarding the teaching of this feature that the L sections of the capture probes are complementary to non-overlapping regions of the label probe, Claimant's position is that 'non-overlapping' must be interpreted functionally. The purpose of the capture probes binding to complementary 'non-overlapping regions' of the label probe (or amplifier or pre-amplifier as the case may be) is to gain additional security of binding compared with that of a single capture probe, while achieving the increased specificity of two probes. This follows from the first part of [0207] of the description:

> In a further indirect capture embodiment shown in Figure 4, two adjacent capture probes are incorporated in a probe set targeting a gene of interest. T1 and T2 are designed to be complementary to two unique and adjacent sections on the target nucleic acid. L1 and L2, which can be different or the same, are complementary to two adjacent sections on the label probe. Their binding sections, T, L or both, are designed so that the linkage between the label probe and the target is unstable and tends to fall off at hybridization temperature when only one of the capture probes is in place. Such a design should enable exceptional specificity because the signal-generating label probe can only be attached to the target gene of interest when two independent capture probes both recognize the target and bind to the adjacent sequences or in very close proximity of the target gene.

35. The Claimant argues that, while a complete non-overlapping is presented as a preferred arrangement of the binding sites since it would allow the more stable duplex, nothing in EP572 discloses to the skilled person that a small overlap is not allowed, for instance by specifying that such overlap would be undesirable. In this context, it argues that a small overlap between the sequences of the polynucleotides at stake is acceptable, if said overlap does not prevent the formation of a stable duplex between said polynucleotides.

36. Thus, the Court understands the Claimant to argue that the functionality of the resulting non-overlapping parts of the probes should be considered, rather than requiring complete non-overlap of the complementary regions of the probes. The High Court followed this approach.

37. The Defendant contends that the term 'non-overlapping' requires that there is no overlap at all between the regions of the label probe (or amplifier or preamplifier) that are complementary to the L-sections of the capture probe. For support, Defendant also refers to [0207] that describes the relevant sections of the label probe as 'adjacent sections', which the skilled person understands to be sections that are next to each other and therefore with no overlap. The Defendant points out that the patents do not describe a single embodiment or depict a single figure with an overlap.

38. The Court finds that the term non-overlapping in feature 1(h) is to be interpreted as not allowing any kind of overlap. This already follows from the literal wording of the claim, which the skilled person will understand to refer to sequences which do not have any overlap at all. The patentee chose to use the restrictive term non-overlapping, which has a specific meaning to the skilled person. Two sequences are either non-overlapping or they are overlapping, the latter to a larger or smaller extent. This literal interpretation is confirmed when considering the teaching of the patent specifications. The function of the non-overlapping regions is to create a stable duplex at the core of the matter. There is no single example or passage in the description that allows for partial overlapping sequences for the binding regions of (T1/ T2 and) L1/L2. Also, the figures of the patent are silent on this. To the contrary, in all figures there is no overlap whatsoever.

39. The Claimant's reference to [0102], in particular to the phrase: "*distinct, nonoverlapping sequences in the nucleic acid target*", on which it bases the argument that non-overlapping

must be given a different meaning than 'distinct', the former thus allowing for some overlap, does not change the interpretation set out in the previous paragraph. This argument, which is materially convincingly refuted by the Defendant, is rejected already for the reason that it is based on a part of the descriptions that does not relate to the hybridisation of the L sections of the capture probes to the label probe (claimed in feature 1.(h)), but only to the binding of the T sections of the capture probes and the target (feature 1.(g)).

Feature 1(j): "*capturing the label probe to two or more capture probes, thereby capturing the label probe to the nucleic acid target*"

40. The Court understands the Defendant to argue in the context of claim interpretation that this feature should be interpreted to also require that the binding of only one capture probe to the label probe is weaker than the binding of two capturing probes to the label probe. Allegedly, the skilled person understands this in view of the disclosure in [0207] of EP572: "…*Their binding sections, T, L or both, are designed so that the linkage between the label probe and the target is unstable and tends to fall off at hybridization temperature when only one of the capture probes is in place. Such a design should enable exceptional specificity because the signal generating label probe can only be attached to the target gene of interest when two independent capture probes both recognize the target and bind to the adjacent sequences or in very close proximity of the target gene*…". In the context of added matter, the Defendant argues that the omission of this disclosure amounts to added matter (this is addressed below).

41. As these specific properties are not explicitly claimed, it is not appropriate to read these into the claim. Feature 1(j) therefore only requires that the label probe captures two or more capture probes, thereby indirectly capturing the nucleic acid target, according to the three different embodiments described in 1(k)(i)-(iii).

Feature 1(k)(i): "*by <u>simultaneously</u> hybridizing at least two different capture probes to a single copy of the label probe*"

42. This feature teaches that two capture probes bind the target to one label probe, creating a so-called cruciform structure. This is at the core of the teaching of the patent as this increases specificity of the assay and reduces background noise, as discussed above. Features 1(k)(ii) and 1(k)(iii) refer to cruciform structures where one (pre-)amplifier binds to two capture probes of the invention.

43. The Defendant argues that 'simultaneously' in this feature requires that the label probe must bind to two capture probes bound to the target at exactly the same instance/time. If the capture of the two capture probes was not simultaneous there would be a period in which only one capture probe was bound. This would be a weak binding according to the teaching of the patents which might not survive the hybridization process. The goal of the invention would thus not be achieved, according to the Defendant.

44. The Claimant correctly refers to [0117] of EP572 (see 5. above, [0112] of EP439), where it is mentioned that '*The various capture and hybridization steps can be performed simultaneously or sequentially*'. Several steps of the method are described in this paragraph. Interpreting feature 1.(k)(i) in conjunction with this paragraph of the description, the skilled person

understands that 'simultaneously' should be read to mean during the same step of the method, in this case during the hybridization step prior to the wash process. The feature thus requires that the label probe simultaneously binds to two different (adjacent) capture probes at the end of the hybridization step.

III.C – VALIDITY

Overview

45. The Defendant asserts that the patents contain added matter and are insufficiently disclosed.

46. The Defendant also considers the patents to lack novelty and inventive step. It cited many prior art documents as relevant for inventive stap attacks in three categories. The Court will only discuss those documents that were presented as the most promising of each category. These are also the documents on which the debate of the parties focussed. These documents are listed below. Furthermore, for inventive step, the Defendant relies heavily on the combination of the cited documents with what is asserts to be CGK of the skilled person. This alleged CGK goes beyond what has been agreed as CGK by the parties (see 30. above) and Claimant disputes that this was CGK at the priority date. It cannot be established that what Defendant asserts to be additional CGK, is to be considered as such.

47. For the novelty and/or inventive step attacks, the following prior art is relevant:

- Collins ML, Irvine B, Tyner D, Fine E, Zayati C, Chang C, Horn T, Ahle D, Detmer J, Shen LP, Kolberg J, Bushnell S, Urdea MS, Ho DD., *A branched DNA signal amplification assay for quantification of nucleic acid targets below 100* molecules/ml. Nucleic Acids Res. 1997 Aug 1;25(15):2979-84, "**Collins**", submitted as exhibit D49[2];
- Kern D, Collins M, Fultz T, Detmer J, Hamren S, Peterkin JJ, Sheridan P, Urdea M, White R, Yeghiazarian T, Todd J. *An enhanced-sensitivity branched-DNA assay for quantification of human immunodeficiency virus type 1 RNA in plasma*. J Clin Microbiol. 1996 Dec;34(12):3196-202, "**Kern**", exhibit D48
- US patent 5,635,352 published on 3 June 1997, "**Urdea**", submitted in these proceedings as exhibit D66
- International patent application WO01/9463 A2, published on 13 December 2001, exhibit D72, "the **Kenny patent"** and Kenny D et al. Detection of viral infection and gene expression in clinical tissue specimens using branched DNA (bDNA) in situ hybridization. J Histochem Cytochem. 2002 Sep;50(9):1219-27, exhibit D24, `'the **Kenny paper**", collectively "**Kenny**",

48. Below, the various validity attacks will be assessed. For each prior art document relied on, the assessment of novelty and inventive step are combined. For the assessment of novelty, the Court will apply the so-called 'gold standard': a prior art disclosure is novelty destroying in case the skilled person would derive the claimed invention directly and unambiguously using common general knowledge, from the prior disclosure, whereby implicitly disclosed subject-matter, i.e. matter that is a clear and unambiguous consequence of what is explicitly mentioned, shall also be considered as part of its content. Furthermore, in assessing novelty,

[2] The Defendant originally submitted separately numbered exhibits with it SoD and its CC, which contained considerable overlap (i.e. many exhibits were submitted twice with different numbers. The numbers used in this decision refer to new combined exhibit numbers for both claim and counterclaim, provided at the request of the Court.

it is not possible to combine different passages or embodiments of a prior art document, except if the corresponding combination is derivable directly and unambiguously by the skilled person reading this document.

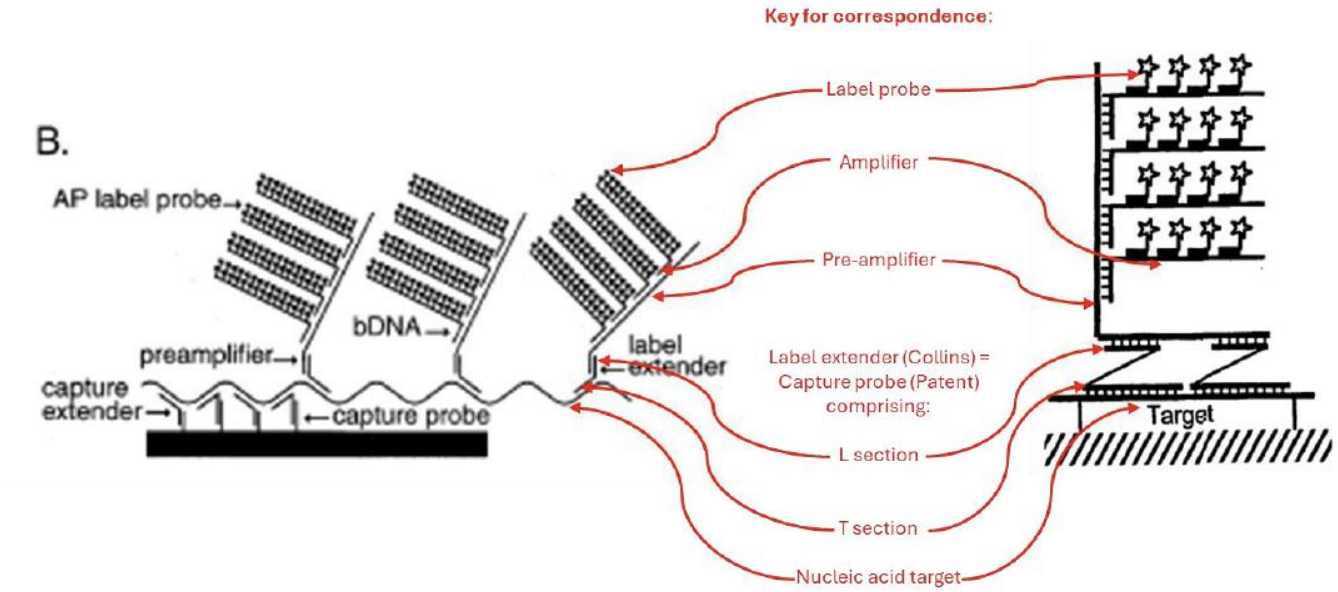
49. For the assessment of inventive step, the parties in theory agreed that the principles set out by the CD Munich in the Amgen v. Regeneron/Sanofi decision (UPC_1/2023 of 16 July 2024) should be applied. This decision mentions in 8.8: "*In general, a claimed solution is obvious if, starting from the prior art, the skilled person would be* ***motivated*** *(i.e. have an* ***incentive*** *or in German: "Veranlassung", see the CoA in NanoString/10x Genomics, p. 34) to consider the claimed solution and to implement it as a* ***next step*** *("nächster Schritt", CoA in NanoString/10x Genomics, p. 35, second par.) in developing the prior art."* In practice the parties rather seem to have applied a test that seems closer to the problem solutions approach. As in this case, the result does not depend on the specific test and as the cited sentence seems to apply to both, the Court will apply principles that are common to both tools for assessing inventive step below.

Collins – novelty and inventive step

50. The Defendant asserts that claim 1 of EP572 lacks novelty in view of Collins and alternatively that novelty of this claim is lacking in view of the combined disclosure of Collins and Kern. Based on the same disclosures, claim 3 of EP439 lacks novelty. Alternatively, it argues that the referenced claims lack inventive step starting from Collins.

51. Collins, a scientific paper published in 1997, describes a bDNA assay for the quantification of nucleic acid target sequences. The contribution of Collins is that is describes a bDNA hybridization assay that has been improved by the inclusion of the novel modified nucleotides, isoC and isoG (to substitute C, cytosine, and G, guanine) in the amplification sequences to prevent non-specific hybridization/binding (abbreviated as NSB in Collins). This assay is referred to as system 8 (bDNA assay). The novel isoC, isoG-containing amplification sequences have no detectable interaction with any natural DNA sequence. Collins found, testing in an *in vitro* context, that non-specific hybridization is reduced by the use of isoC and isoG, improving sensitivity of the assay.

52. The Defendant relies on figure 1B of Collins for its novelty attack, which is depicted below (on the left) as shown in the counterclaim for revocation, together with fig. 4 of the patents (on the right) and with red markings added by the Defendant.



53. According to the nomenclature of Collins, capture probes and capture extenders (CE) are oligonucleotides used for in vitro assays to capture the nucleic acid target to the solid support (page 2979, Introduction, left column). These are not required for ISH assays because the nucleic acid target is fixed (cross-linked to the sample) in that type of assay, as described by the Defendant. Parties also agree that what is referred to as the 'label extender' in Collins corresponds to a capture probe of the claimed inventions. The 'label extender' (abbreviated as LE in Collins LE's has a T and an L section, as indicated in the figure above in red.

54. The assays disclosed in Collins are, as mentioned, *in vitro* assays and not ISH (*in situ*). Feature 1(a)-(c) of EP572 are therefore not disclosed. The assays shown in Figure 1B of Collins all use a single LE, which binds to a LE/capture probe. It therefore does not disclose that for each nucleic acid target two or more different capture probes are used (feature 1(e)). As there is only one capture probe, all features relating thereto, including the cruciform structure of 1.k(i) (or (ii) and (iii)), are not disclosed in Collins.

55. The Defendant relies on the Discussion paragraph of Collins wherein several options are discussed for which the system 8 assay could be used. In this context ISH/in situ and cruciform design are mentioned. The Defendant relies on the following parts of the discussion:

> "*In theory, the system 8 bDNA assay can be made considerably more sensitive (…) by increasing the S/N ratio. Most of the background is coming from LE NSB [label extender non-specific binding] and amplifier NSB (data not shown). By using cruciform LEs, a design in which two LE probes must bind the target in the correct orientation to bridge the preamplifier, most of the LE NSB can in theory be removed (18)*" [wherein footnote 18 refers to Kern, the Court]
>
> and
>
> "*The system 8 bDNA assay should also be useful in other hybridization assays. In both filter and in situ hybridization assays, for example, billions of overlapping, unique oligonucleotide sequences are available for possible NSH to probes. The ability to amplify the signal without amplifying noise from hybridization of amplification molecules to sample nucleic acid sequences should greatly improve the sensitivity of these assays. Currently, in situ PCR is the standard for detection of single copy DNA sequences in cells (28,29); in situ RT–PCR has occasionally been problematic for mRNA detection (30–33). RNA targets that are partially degraded or intramolecularly crosslinked at selected sites*

should pose no special problems for in situ bDNA assays since priming and reverse transcription are not required. As in assays that target DNA, multiple oligonucleotides will be used to label target RNA in cells; failure to bind one or more of these oligonucleotides is of no real consequence. Quantification may also be possible with the in situ bDNA assay with proper selection of internal standards. The sensitivity of the system 8 bDNA filter and in situ hybridization assays should be limited mostly by the specificity of the oligonucleotide probes. Empirical selection of the best LE oligonucleotide probes and the use of the cruciform design (18) should prove most useful in optimizing specificity."

56. The Claimant rightly points out that the options mentioned in the discussion of Collins for further possible uses of the system 8 assay, are theoretical; the options are referred to as 'in theory' or as 'should be useful'. Furthermore, in the discussion section *in situ* and the use of a cruciform structure are mentioned as two of several possibilities to further apply or to improve the system 8 assay, with none of the options being mentioned as preferred. Claimant asserts that thirteen different options are mentioned in the discussion. In any case, the following four options are included (i) applying the *in vitro* system 8 bDNA assay to filter hybridization or to (ii) *in situ* hybridization and (iii) improving the specificity of the assay by the empirical selection of the best LE oligonucleotides or (iv) by the use of a cruciform design. For disclosure of the claimed subject matter, the skilled person would have to choose to read options (ii) and (iv) into the embodiment of figure 1B of Collins. This does not amount to a direct and unambiguous disclosure of claim 1 of EP572.

57. For these reasons Collins is not novelty destroying. Since the subject matter of claim 1 is novel, the same applies to the dependant claims. The same considerations also apply to claim 3 of EP 439.

58. For lack of novelty, the Defendant in addition relies on the combination of Collins and Kern. Kern describes the development of cruciform probes in the second-generation bDNA assays. For lack of novelty, it is impermissible to combine separate items of prior art unless there is a specific reference in one prior art document to a second prior art document enabling the skilled person to construe the two documents as a single disclosure. Such incorporation has been for instance accepted when a second document is referred to for a specific method of preparation of a certain component described in the referenced document. In the present case, the general reference to Kern for support that the use of cruciform LEs can *in theory* remove most of the LE NSB (see the relevant sentence at the end of the first paragraph cited in 55. above), is not considered to meet these strict criteria, as Claimant correctly points out. This combination-novelty-attack is therefore not accepted.

59. In the context of inventive step, the technical differences between Collins and the claimed inventions are at least (i) that the claimed method relates to an *in situ* situation and (ii) that a cruciform design with two capture probes is applied to increase specificity/reduce 'background noise' caused by non-specific binding (NSB). As discussed above, Collins discloses an *in vitro* assay wherein modified nucleotides (isoG and isoC) are used to increase specificity instead of a cruciform design. Even if Collins can be considered a reasonable starting point for the assessment of inventive step, the Court finds that there was no incentive to modify the embodiment disclosed in Figure 1B of Collins to come to the claimed inventions. To arrive at the claimed invention, (at least) two amendments would have to be made to the disclosure of Collins, i.e. shifting from *in vitro* to *in situ* and applying a cruciform design. Claimant and its experts explained convincingly that, while there was a great interest at the time (involving a lot of research) to develop *in situ* assays with high specificity, the relevance of the use of cruciform structures in this context was made obsolete by the disclosure of Collins that teaches

to make use of modified nucleotides for that purpose instead, which was considered a simpler system. In other words, the implementation *in situ* of the finding of Collins that isoG and isoC-substituted nucleotides were effective to considerably reduce NSB, was the new direction of research for *in situ* assays at the time. Prior art document Kenny, discussed below, is illustrative of this. In this respect, Collins rather teaches away from the use of a cruciform probe design of the inventions, also for an *in situ* context. Furthermore, contrary to what the Defendant asserts, the use of cruciform bDNA in *in situ* assays was not CGK at the priority date, contrary to the use of bDNA as such. There is no single reference cited by the parties that any kind of cruciform design had been used in *in situ* settings before the priority date and the alleged suggestion in Collins for a cruciform design in an *in situ* context was apparently not followed, although Collins was published nine years before the priority dates. Combining Collins with CGK and/or Kern does not alter this.

60. Collins, alone or in combination, therefore does not prejudice the inventiveness of the independent claims of the claimed inventions. In view of this outcome, the arguments on the dependent claims do not need to be considered.

Urdea - novelty and inventive step

61. The kit of claim 1 of EP439 is submitted to lack novelty, alternatively inventive step, in view of Urdea (for which patent Collins is cited as (co)inventor), because of what is disclosed in example 2 thereof. Urdea is also relied on for an inventive step attack on claim 1 of EP572 and claim 3 of EP439. Urdea is considered the most promising starting point in the category of prior art documents concerning the use of cruciform capture probes in an *in vitro* context. Urdea, first published in 1997, describes solution-phase (also defined as *in vitro*) sandwich hybridisation assays with an aim to improve these by reducing non-specific hybridisation and non-specific binding to increase the signal-to-noise ratio.

62. The Defendant asserts that Urdea, discloses, apart from *in situ*, all features of claim 1 of EP439 in the embodiment of example 2, column 22 line 54-column 23 line 9 and figure 11, depicted below. The figure shows two label extenders (LE1 and LE2) which are capture probes in the nomenclature of the patents, that both bind to the target polynucleotide and do so in a cruciform arrangement with the preamplifier.

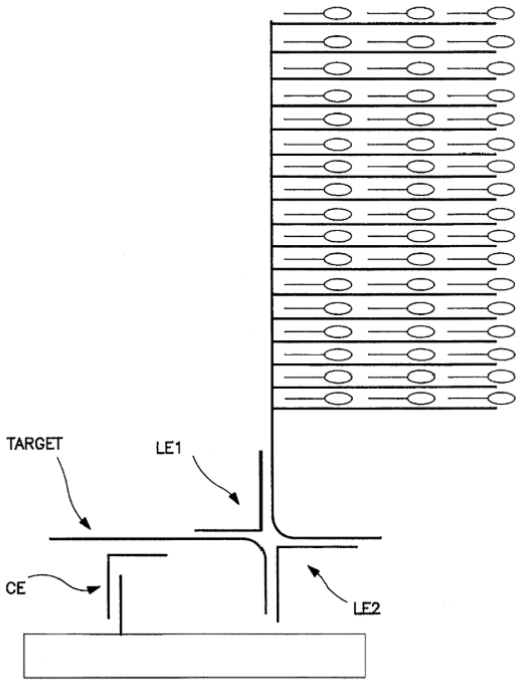


FIG. 11

63. Claim 1 of EP439 is directed at 'a kit or detecting a nucleic acid in an individual cell'. This wording only requires that the kit must be suitable for detecting a nucleic acid in an individual cell, i.e. in *situ.* Defendant asserts that this is the case because example 2 is said to contain reagents for sample preparation, including proteinase, with reference to column 27 lines 8-13 of Urdea:

> *"Sample preparation consisted of delivering 150 µl P-K Buffer (3.3 mg/ml proteinase K in 58 mM Tris-HCl, pH 8.0/0.6M NaCl/0.06M sodium citrate/12 mM EDTA, pH 8.0/1.3%SDS/16 µg/ml sonicated salmon sperm DNA/7% formamide/100 fmoles capture extender probes/400 fmoles label extender probes) to each well."*

This illustrates that the reagents necessary for carrying out the assay include both proteinase K and SDS. Both are reagents suitable for permeabilising cells. This formed part of the common general knowledge and is confirmed in the description of the patents, which includes a section entitled "Permeation" that states:

> *"Detergents (e.g., Triton X-100 or SDS) and Proteinase K can also be used to increase the permeability of the fixed cells. Detergent treatment, usually with Triton X-100 or SDS, is frequently used to permeate the membranes by extracting the lipids. Proteinase K is a nonspecific protease that is active over a wide pH range and is not easily inactivated. It is used to digest proteins that surround the target mRNA."* ([0203] of EP572)

The Defendant contends that this qualifies as 'at least one reagent for permeabilising cells' of feature1(b) of claim 1 of EP439.

64. The Claimant disputes that Urdea is novelty destroying. As was discussed during the oral hearing, the disclosure relied on is not suitable for *in situ* use, because the skilled person recognises that the conditions described in example 2 of Urdea are too harsh for permeabilization in an *in situ* context, i.e. the conditions disclosed in example 2 of Urdea are not suitable for an *in situ* assay. In the Court's view, Urdea is therefore not novelty destroying for claim 1 of EP439.

65. The Defendant also bases on Urdea inventive step attacks for claims 1 of the patents and claim 3 of EP439. The Court considers the patents inventive over Urdea for the following reasons.

66. Although Urdea relates only to *in vitro* assays and the claimed invention relates to *in situ* tests, Urdea is considered a realistic starting point for the skilled person aiming to develop *in situ* tests, since the relevant skilled person has knowledge of both *in vitro* and *in situ* tests.

67. As mentioned above, Figure 11 of Urdea discloses a cruciform design with two label extenders (capture probes). Urdea also discloses the non-overlapping features in the paragraph bridging columns 14 and 15. This is not in dispute. The parties hence agree that (in the embodiment of example 2/figure 11 of) Urdea discloses all features of claim 1 of EP572 except for the *in situ* use.

68. In view of the difference between the disclosure of the Urdea patent and the claimed subject matter and in view of the disclosure of the patents in dispute (see e.g. paragraph [0010] of EP572), the objective technical problem is the provision of methods for detecting and identifying rare nucleotides in individual cells, i.e. an *in situ* assay, with high specificity.

69. The Court considers that the skilled person would not apply the teaching of Urdea in an *in situ* context, although in theory that person could have done so, firstly because, as observed by the Claimant, Urdea discloses numerous embodiments of an assay, most of which do not apply the cruciform design. A cruciform design is only used in the embodiments of Figures 11 and 8, wherein the latter embodiment has a different design with capture probes that do not bind to both the target nucleic acid and the label probe/amplifier or preamplifier. Thus, only when starting from Figure 11 it might be possible to arrive at the claimed invention. However, it is not clear why the skilled person aiming to solve the above technical problem would start with the embodiment of Figure 11 of Urdea with a cruciform structure, and not for instance with another of the test designs which are also disclosed in Urdea. There is no pointer in Urdea that gives any motivation to the skilled person to apply the disclosure of example 2/figure 11 in an *in situ* context. The Defendant refers to the general statement that "*the techniques of the present invention may be used in conjunction with a wide variety of assay formats*". As correctly observed by the Claimant during the oral hearing, these passages do not mention *in situ* and might well have been understood as referring to various *in vitro* formats, in particular combinations of embodiments disclosed in Urdea itself. In any case, this general statement does not specify example 2/figure 11 for *in situ* use.

70. Secondly, as highlighted by Claimant's expert Dr. Urdea, both in his declaration and during the oral hearing, the approach of utilizing the setting of example 2/figure 11 of Urdea *in situ,* while increasing specificity, was expected to reduce the signal produced by the assay, because both label extenders/capture probes must bind to the target nucleic acid in order for the bDNA amplification multimer to bind and to produce a signal. This was contrary to the efforts that researchers were making at the time with *in situ* hybridization assays, which were focused on increasing the signal to allow lower copy nucleic acids to be detected. This can be considered to teach away from the use of cruciform designs *in situ*.

71. In view of this foreseen disadvantage of the specific cruciform design *in situ,* it is of no relevance for the assessment of inventive step in the present case that for non-cruciform designs (not having the problem of reduced signal production) similar designs were successfully applied in both an *in vitro* and an *in situ* context (see for instance prior art references submitted by Defendant as exhibits D23, D41, D42, D43, D51 and D52, all relating to non-cruciform designs). This is in particular so, as explained in the declaration of

Claimant's expert Dr Wolf (exhibit ACD40, para 3.10-3.13), because, as was known at the priority date, non-specific binding is a much more significant concern for *in situ* assays, because of the presence of a high number of non-target nucleic acids as these cannot be washed away or otherwise prepared to create 'clean' samples as is done for *in vitro* assays. The use of modified nucleotides, as proposed by Collins, was expected to significantly reduce binding to non-target nucleic acids at the priority date. The effect of cruciform bDNA in this respect was not yet known.

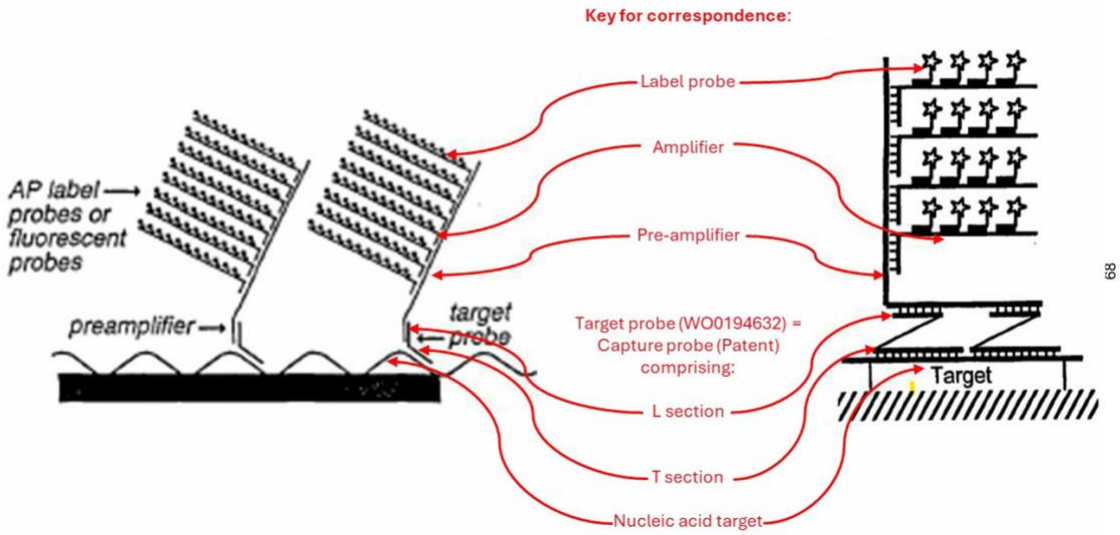
72. Thirdly, it is to be noted that Urdea was published nine years before the priority date of the patents. There is no evidence on file that any type of cruciform design was used or at least suggested for an *in situ* setting before the priority date. While a time lapse of nine years in itself does not necessarily lead to a conclusion of inventive activity, it still illustrates that cruciform designs were not considered for an *in situ* context, although the technical field at issue to find suitable, specific *in situ* assays was highly competitive, as also mentioned in the context of Collins at 59 above.

73. Even though it might be true that in general, at the priority date, it was obvious for the skilled person to make an effort to adapt *in vitro* assays to an *in situ* environment, the Court concludes that at the priority date it was not obvious for a skilled person to arrive at the claimed invention, starting from Urdea.

Kenny – inventive step

74. The Kenny patent, published in December 2001, is relied on as a representative disclosure of a bDNA ISH in the prior art. Kenny does not disclose the use of a cruciform structure. Kenny confirms that the bDNA technology can be used *in situ,* with results similar to those found by others previously. It discusses the use of isoC and isoG non-natural nucleotides (to prevent NSB), as used in Collins.

75. Figure 1 of Kenny is shown together with figure 8C of the patents and with red markings added by the Defendant, as depicted in the counterclaim submission (at 259):



76. The difference with claim 1 of EP572, is the requirement that at least two different capture probes simultaneously hybridize to a single copy of the preamplifier, i.e. of a cruciform capture

probe arrangement. The Defendant asserts that it would be obvious for the skilled person to add this. For the reasons set out above with respect to Collins and Urdea, the Court finds that it was not obvious at the priority date for the skilled person to adapt a system that uses modified bDNA to increase specificity to a completely different system using a cruciform design. The combination with Collins will not change this, also in view of the above. As pointed out by the Claimant, the skilled person was furthermore aware of the general challenges of *in situ* assays compared to *in vitro* assays, making that person even less inclined to pursue the cruciform alternative *in situ* to improve a modified bDNA assay. In the related Kenny paper, on which the Defendant also relies, this is described as follows:

> *"However, the sensitive detection of nucleic acid sequences in tissue biopsy specimens has proven more challenging. In addition to the general problems of ISH, such as diffusion of signal fluorescence quenching, and preservation of cell morphology, effective detection of nucleic acid sequences in biopsy specimens must overcome challenges unique to tissue sections including more limited accessibility to target sequences, increased background from non-specific hybridization, endogenous reporter activity, and preservation of complex tissue architecture*." (the Kenny paper, p.1220, left column)

There was thus no incentive to amend an *in situ* assay wherein modified bDNA was used to increase specificity, to the use of a cruciform design for that purpose of which the effectiveness *in situ* was not obvious at the priority date.

Insufficiency of disclosure

77. The Defendant raises the insufficiency objection as a squeeze for inventive step. To the extent that any feature of the claims is alleged not to be reproducible from the prior art, taking into account the common general knowledge, there is a corresponding lack of sufficiency of disclosure in the patents. In summary, it is argued that the patents are not more enabled than the prior art.

78. The above assessment on inventive step does not result in a squeeze situation since it is not part of the reasoning that the prior art was not enabled or created a prejudice. In any case, the defendant has not substantiated its allegations, therefore the insufficiency objection fails.

Added matter

79. The test for added matter is the same gold standard as set out above for novelty. There is added matter if the claim as granted contains subject-matter that extends beyond the content of the application as filed. In order to assess whether there is added matter, the Court must thus first ascertain what the skilled person would derive directly and unambiguously using common general knowledge and seen objectively and relative to the date of filing, from the whole of the application as filed, whereby implicitly disclosed subject-matter, i.e. matter that is a clear and unambiguous consequence of what is explicitly mentioned, shall also be considered as part of its content.[3]

The Independent claims

80. The Defendant is of the view that independent claim 1 of EP572 and independent claims 1 and 3 of EP439 contain added matter.

[3] See CoA decision of 2 October 2025, UPC_CFI_764 and 774/2024 (expert Klein)

81. The only disclosure relevant for the claimed specific relationship in claim 1 of EP572 between 'nucleic acid target', 'two or more capture probes' and one 'label probe' (or amplifier/preamplifier) is in [0202] of WO986 (the application as filed, Exhibit D78) relating to the embodiment of figure 4. There are, according to Defendant, several reasons why this disclosure does not provide basis for the specific relationship defined in claim 1, resulting in several added matter issues, discussed below.

82. The main alleged issue is that in (features 1(g) and 1(h) of) claim 1 of EP572, the term 'non-overlapping regions' is used to describe the complementarity of T and L sections of the capture probe to, respectively, the nucleic acid target and the label probe However, [0202] of WO986 discloses:

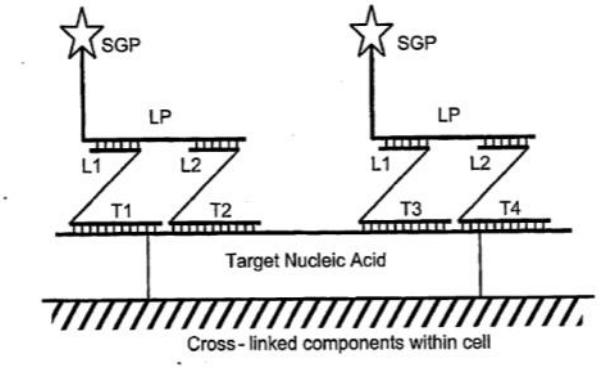
> "T1 and T2 are designed to be complementary to two unique and adjacent sections on the target nucleic acid. L1 and L2, which can be different or the same, are complementary to two adjacent sections on the label probe".

In this passage the term 'non-overlapping' is not used but the phrases 'two unique and adjacent sections' or 'two adjacent sections'. According to the Defendant 'non-overlapping regions' does not have the same meaning as either 'two unique and adjacent sections' or 'two adjacent sections'. Even if the difference in the terms 'section' and 'region' is overlooked, in the context of polynucleotides, 'non-overlapping' sequences need not be 'unique' or 'adjacent' and therefore the term non-overlapping has a broader meaning. The Defendant points out that this is confirmed by claim 2 as granted (which is dependent on claim 1 as granted) which requires that "*the two or more different capture probes hybridize to unique and adjacent sections on the nucleic acid target*." As claim 2, being a dependent claim, must limit the scope of claim 1, the presence of this claim in the claim set confirms that non-overlapping has a broader meaning. Paragraph [0202] of WO986 (which is limited to 'unique and adjacent sections') thus cannot provide basis for (features 1(g) and (h) of) claim 1 of EP572. The same applies to the corresponding features 1(f) and 3(e) of independent claims 1 and 3 of EP439.

83. The Court finds explicit basis for feature 1(g) of EP572 in [0018] and [0098] of WO986:

> *[0098] In embodiments in which two or more first capture probes and/or two or more second capture probes are employed, the capture probes preferably hybridize to nonoverlapping polynucleotide sequences in their respective nucleic acid target. (…) For a given nucleic acid target, the corresponding capture probes and blocking probes are preferably complementary to physically distinct, nonoverlapping sequences in the nucleic acid target, which nonoverlapping sequences are preferably, but not necessarily, contiguous.*
> [note: the text of [0018] is identical to the first sentence of [0098]]

Here the term non-overlapping is used to describe the complementarity of the T sections and the target. This non-overlapping feature can also be derived from figures 4, 5, 6A, 7, 8 and 9 of WO986 (which are identical to the figures of the patents). For feature 1(h), which teaches that the at least two capture probes hybridize to non-overlapping regions of the label probe, no *expressis verbis* basis can be found in the original application as filed. However, in all figures in which at least two capture probes bind to the label probe, this binding is to non-overlapping regions. For instance, from figure 4, replicated once more below, it can be derived that the binding/hybridisation of the L sections of the capture probe is to non-overlapping sections of the label probe LP.



The same is true for figures 5, 6A, 7 and 8. Thus, when considering the disclosure on the definition of the binding of the capture probes to the target as well as the depiction of the binding of the capture probes to the label probe, the skilled person derives from the original application that also the binding to the capture probe is to non-overlapping regions. Moreover, for the binding of the capture probe to the target not only the term binding to '*non-overlapping*' regions is used but also the term binding to *'(unique) and adjacent*' regions (paragraph [0202] of WO986). The same term '*adjacent*' is also used in paragraph [0202] of WO986 when defining the binding of the capture probe to the label probe. From this, the skilled person understands that the binding of capture probes to the label probe is essentially the same as to the target in that it is to non-overlapping regions. As mentioned, according to figures 4, 5, 6A, 7 and 8 the non-overlapping parts are close but not directly adjacent. This also provides basis to define the regions with the broader term 'non-overlapping' in claim 1 and then use the narrower term 'adjacent' in claim 2 as granted. The skilled person will derive this directly and unambiguously from the application as filed, using his common general knowledge. Consequently, there is no impermissible broadening.

84. The Defendant also asserts added matter in that [0202] of WO986 defines the capture probes as being designed "*so that the linkage between the label probe and the target is unstable and tends to fall off at hybridization temperature when only one of the capture probes is in place."* This feature is missing in claim 1 as well as the functional feature of the 'indirect capture'. Moreover, paragraph [0202] of WO986 concludes by stipulating: "*In the same way, the linkage between the label probe and the target can only survive the hybridization when both capture probes are hybridized to the target in a cooperative fashion*." The term 'cooperative fashion' is an essential feature of the embodiment disclosed in paragraph [0202] of WO986 and its omission results in added matter, according to Defendant.

85. The Court considers these additional features, partly the subject of subclaims, to be optional, and not inextricably linked to the claimed features. While paragraph [0202] of WO986 contains functional language on the instability of the binding of the label probe to just one capture probe as well as the feature of a cooperative binding., other paragraphs of WO986 referred to by the Claimant do not contain this limitation, in particular paragraphs in the general part of the description (e.g. [0015] and [0016]). In [0088] cooperative binding is specifically referred to as 'optional'. The patentee did not include these options in the claim, which only require simultaneous binding, the subject of feature 1(k), leaving open the underlying technique by which this is achieved (e.g. instability of the binding of one capture probe, cooperative binding).

86. The alleged omission of the feature of indirect capturing, has no factual basis as the claim language relates to indirect capturing: it already follows from the use of a capture probe (as

defined in [0081] of WO986) that the label probe (or (pre)amplifier, as the case may be) does not bind directly to the target nucleic acid. The skilled person will derive this directly and unambiguously from, for instance, the wording of the claim, the definition of the capture probe as binding to both the target and the label probe and the figures.

87. Several further assertions of added matter in relation to figure 4 and [0202] of WO986 are not convincing; these seem farfetched and not based on a reading of the complete application with a mind willing to understand. As correctly observed by the Claimant, WO986 not only discloses multiplexing wherein two capture probe sets are used to target two different targets in one assay (e.g. figure 4), but also the possibility to use only one capture probe set to detect one target (see e.g. figures 6b, 7 and 8 and paragraphs [0018] and [0098] of WO986). Thus, contrary to what the Defendant argues, there is no need to limit the claim to the use of two (or more) capture probe set. The claim is not limited to the embodiment of figure 4 (as described in [0202]). This is already apparent from the fact that not only indirect binding of the label probe to the target through binding to capture probes is claimed, but also via amplifiers and/or pre-amplifiers, as explicitly disclosed in for instance [0088]. This paragraph is also a basis for the binding of just one label probe to an amplifier or preamplifier since the term label probe is used in the singular. The original application furthermore does not require that the capture probes have the same orientation (e.g. paragraphs [0081] and [0101] of WO986 are silent on this requirement). Contrary to what the Defendant asserts, this does not follow from the fact that the capture probes in figure 4 all have the same 5'-3' orientation.

88. In addition, it is argued with respect to the relationship between the label probe, the amplifier and the preamplifier, that the claim also covers the embodiment that only one label probe binds to the amplifier or preamplifier. This 1:1 ratio does not result in amplification of the signal, which according to the Defendant runs contrary to the clear teaching of WO986 in [0088]. As set out above, the teaching of the patent is primarily to increase the specificity of the detection of low quantities of nucleic acid sequences in cells. It follows from WO986 that amplification of the signal in that context is optional; this occurs when (pre)amplifiers are involved and not in the first embodiment with only a label probe.

89. The Defendant also argues regarding independent claim 3 of EP439 that the term "*sample of fixed and permeabilized cells*" therein adds matter. Whilst different types of samples are mentioned, this is only in the context of methods. There is no indication in WO986 that the disclosure is directed to 'a sample' per se and, as such, claims directed to samples present the skilled person with new technical information that is not directly and unambiguously derivable from the application as filed. By way of example, Defendant refers to paragraph [0024] of WO986.

90. In the Court's view also a sample as such is clearly derivable from WO986. Paragraph [0024] reads "*The methods can be used to detect the presence of the nucleic acid target in cells from essentially any type of sample. (…) Thus, in one class of embodiments, the methods include identifying the cell as a desired target cell based on detection of the first and second signals (and optional third, fourth, etc. signals) from within the cell*. *As just a few examples, the cell can be a circulating tumor cell, a virally infected cell, a fetal cell in maternal blood, a bacterial cell or other microorganism in a biological sample, or an endothelial cell, precursor endothelial cell, or myocardial cell in blood*." While samples are mentioned in the context of a method, this qualifies as a disclosure of a sample as such as an indispensable part of the method. In addition, paragraph [0162] cited by the Claimant, under the header '*Compositions and Kits*' provides a

clear indication that samples as such were considered by the applicant to be part of the invention. It is stated: "*The invention also provides compositions useful in practicing or produced by the methods. One exemplary class of embodiments provides a composition that includes a fixed and permeabilized cell, which cell comprises or is suspected of comprising a first nucleic acid target and a second nucleic acid target, at least a first capture probe capable of hybridizing to the first nucleic acid target, at least a second capture probe capable of hybridizing to the second nucleic acid target, a first label probe comprising a first label, and a second label probe comprising a second label. (…)*". While this passage does not specifically use the word sample, it is still clear that the disclosure of the invention in WO986 is not limited to methods but includes also compositions produced by the method. The described exemplary composition has several of the features of the sample of claim 3 of EP439.

91. All added matter arguments raised for claim 1 of EP 572 are therefore dismissed. For the same reasons summarized for claim 1 of EP572, the Court considers that the corresponding features of independent claims 1 and 3 of EP439 do not contain added matter.

The dependent claims

92. In the counterclaim for revocation, the Defendant raised added matter objections to almost all dependent claims of EP572, in particular also to claims 2-9 of EP572 which were not invoked by the Claimant in the infringement action, as well as to all dependant claims of EP439. It asserts that each of these dependent claims introduce new technical information that is not present in the application as filed. The Claimant contested all these added matter attacks in the defence to the counterclaim in a substantiated way, referring to specific paragraphs of WO986 where the relevant information can be found. In its reply to this defence, the Defendant did not respond to any of these added matter rebuttals. It focused on novelty and inventive step attacks instead. In the introduction to its reply, the Defendant mentions that it intends '*to avoid repetition of the Defendant's previous submission. Instead, the Defendant has sought to address what it considers to be the more relevant issues and new arguments. By not addressing every statement within the Claimant's documents, it should not be taken as an indication that the Defendant agrees with those statements.'* The (new) arguments raised by the Claimant in the defence to the counterclaim, are obviously not addressed in the Defendant's previous submission. By not providing the Court with any arguments why these added matter arguments do indeed hold, in spite of the parts of WO986 pointed to by Claimant's as a basis for these independent claims, the Court considers these added matter attacks if not forfeited, then in any case, convincingly rebutted by the Claimant. Defendant did not meet its burden of statement and proof in this respect.

Summary on validity

93. As all invalidity attacks are dismissed, EP572 and EP 439 are both valid as granted or amended by the EPO. There is no need to discuss the conditionally filed auxiliary requests.

III.D – INFRINGEMENT

94. In the undisputed product and process description ("PPD") of the HCR Products provided by the Defendant, agreed by parties in parallel UK proceedings, the following is disclosed in Figures 1 and 3:

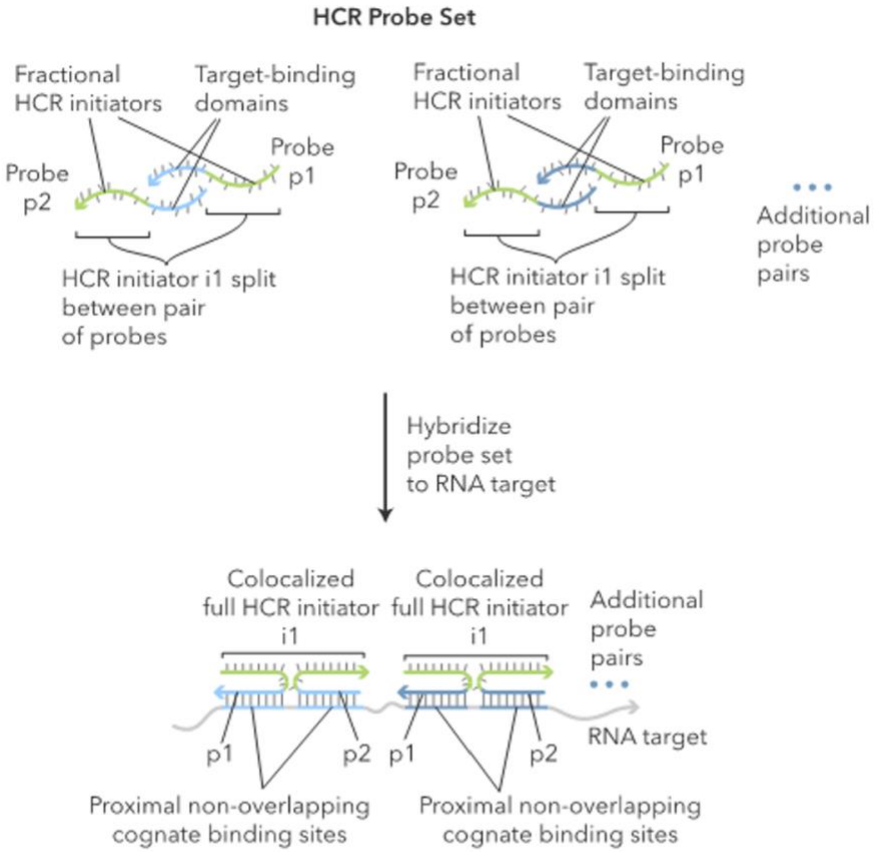


Figure 1. HCR Probe Set.

95. The Claimant convincingly asserts that the probes p1 and p2 can be considered capture probes of the claimed inventions. The blue parts of these initiators/capture probes are the T sections of the capture probe, as they hybridize to regions of the RNA target as required by feature 1(g). In Figure 1 above, top left, these blue regions are referred to as 'target-binding domains'.

96. The green parts of the probes p1 and p2 are referred to as fractional (HCR) initiators (see also Figure 1 above, top left). As the T sections/blue parts of the probes bind to the target at adjacent locations, the green parts of the probes p1 and p2, which are also located next to each other, together form what is referred to in the HCR Protocol (and in the PPD) as '(colocalized) full HCR initiator i1 (and i2)'. The green parts of the capture probes p1 and p2, the fractional initiators, correspond to the L sections of the capture probes of the claimed inventions. These parts can bind to a label probe or amplifier.

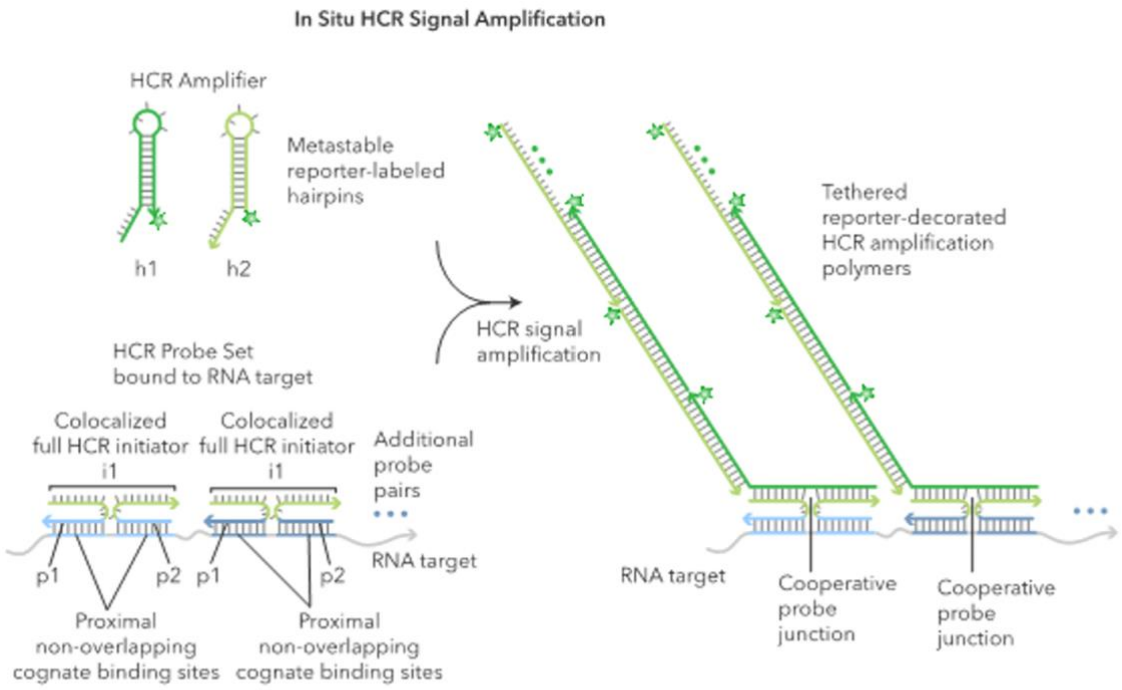
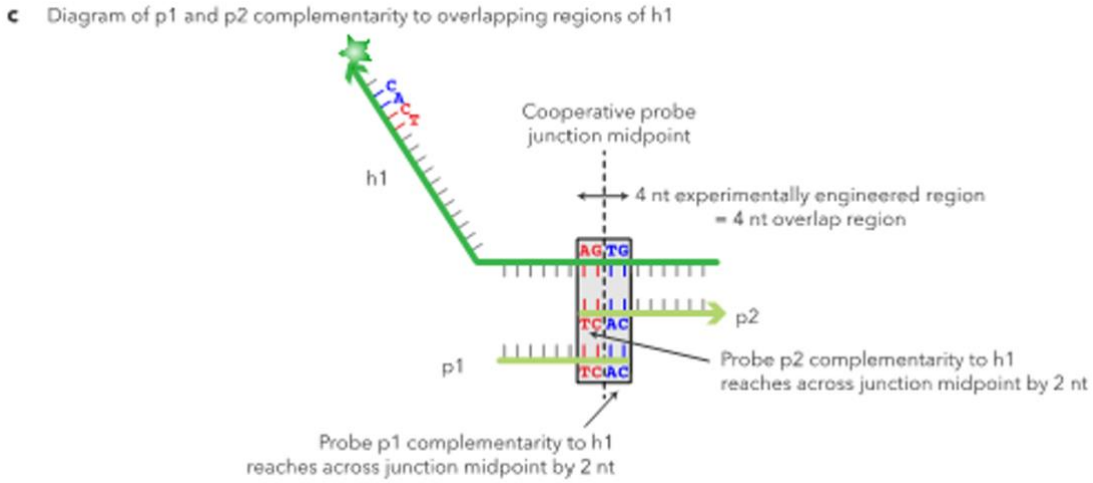


Figure 3. In situ HCR signal amplification.

97. The hairpins h1 and h2 of the HCR Products (shown in Figure 3 above, top left, carry labels (indicated with a star) and correspond to label probes and/or amplifiers of the claimed inventions.

98. According to the HCR Protocol, the label probe/hairpin h1 binds/hybridises to the full HCR initiator, which is formed by the combination of the green parts of the probes p1 and p2. Thereby the hairpin h1 is unfolded. This triggers a signal amplification reaction whereby label/amplifier probe hairpin h2 binds to h1, which binds to another h2 amplifier, which in turn binds to another h1 etc., and thus increasing the strength of HCR signal amplification with each extra (former) hairpin. This is illustrated on the right hand side of Figure 3 above.

99. Figure 7c of the PPD, reproduced below, shows in detail the regions of complementarity between (the green/fractional initiator/L sections of) probes p1 and p2 and the HCR hairpin probe h1. It is apparent from this figure that there is an overlap in the sequences of the fractional HCR initiators (the light green sequences in i1).



100. There is thus an overlap between the regions on the label probe/amplifier/hairpin probe h1 to which the L sections of the capture probes are complementary. The Defendant specified that depending on the specific kit, the overlap is 1, 2, 3 or 4 nucleotides. This is not in dispute.

101. Feature 1(h), '*and the L sections are complementary to nonoverlapping regions of the label probe [or (pre)amplifier]'* as interpreted above, requires that there is no overlap at all between the respective complementary regions on the label probe. The attacked embodiments therefore do not use feature 1(h) of EP572. The same applies to the corresponding features 1(f) and 3(e) of EP 439. Consequently, Defendant does not infringe the independent claims of the patents literally with the HCR Products.

infringement by equivalence?

102. The Claimant asserts that, in case no literal infringement of feature 1 (h) of EP572 (and the corresponding features of EP 439) can be established, there is in any case infringement by equivalence.

103. The Defendant firstly objects (in its rejoinder in the infringement action) to the late introduction of the equivalence argument in these proceedings, in the reply to the statement of defence. It points out that in the proceedings before the High Court, where the same PPD was at issue, the Claimant ran an argument of infringement by equivalence from 23 September 2022. In these specific circumstances, the Claimant ought to have pleaded infringement by equivalence in its SoC dated 22 April 2024. The Defendant also points out that it is prejudiced in its defence because it only has one written round to respond to the equivalence arguments. The pleadings relying on infringement by way of the doctrine of equivalence, is therefore inadmissible.

104. With reference to a CoA order of 21 November 2024 (UPC_CoA_456/2024, OrthoApnea), the Claimant asserts that introducing the equivalence argument in its reply to the SoD is admissible in these proceedings.

105. It follows from the cited CoA order that adding an equivalence argument does not involve an amendment of a case for which judicial leave is required within the meaning of R. 263 RoP as it does not change the nature or scope of the dispute. It thus remains to be assessed whether relying on equivalence first in the statement of reply is in line with R. 13 RoP, which requires that the SoC contains the reasons why the facts relied on constitute an infringement of the

patent claims, including arguments of law, which provision must be interpreted in light of the final sentence of Recital 7 of the Preamble to the Rules of Procedure, which requires parties to set out their case as early as possible in the proceedings. The equivalence arguments (also) in this case are a response to the arguments made by the Defendant in the SoD and are in line with the argumentation on literal infringement presented by the Claimant in the SoC. The equivalence arguments are based on the same patent, are directed against the same HCR Products and relate to claim features that the Claimant has specifically addressed in the SoC. Although it would have been prudent for the Claimant to argue not only literal infringement, but also by equivalence in the SoC, it is understandable that it did not do so in view of the outcome of the High Court proceedings, which outcome was already known at the time of filing of the SoC even though the written judgment was not yet available.

106. The Defendant is not unreasonably prejudiced by the filing of the equivalence arguments in the reply, as it had the opportunity to respond thereto both in writing (in their statement of rejoinder), and orally (at the oral hearing in the main proceedings). Moreover, Defendant could rely on the debate regarding thereto in the parallel UK proceedings.

107. The equivalence arguments introduced in the reply to the SoD are therefore admissible. Although the reasoning in the reply seems to focus on features 1(d)(iii), 1(j) and ((k)(iii) of EP572, the arguments also seem to cover equivalence of feature 1(h), which was also explicitly addressed during the oral hearing and to which the Defendant did not object.

108. Materially, the Court finds that in this case there is no infringement by equivalence with regard to the missing 'non-overlapping' of feature 1(h). First, in view of the legal certainty for third parties, the Court finds it difficult if not impossible to properly construe how much overlap would then still be equivalent. Secondly, while the Court finds the patents valid, it is also clear that they do not form a very significant step in the development of *in situ* assays (very shortly put, all ingredients of the claimed inventions were already known, just not in combination). The fair protection of the patentee therefore does not require a finding of equivalence, especially not if it is weighed against the above-mentioned legal uncertainty on how much overlap is equivalent. Thirdly, the Defendant explained that there is a specific technical reason for the overlap of 1-4 nucleotides. Using probes p1 and p2 comprising fractional initiators that hybridize to partly overlapping regions of HCR hairpin h1 (instead of hybridizing to completely non-overlapping regions of the label probe as advocated by the patents), energetic relaxation of the junction via alternative base pairing in the overlap region reduces the kinetic barrier to branch migration, speeding up the opening of the first h1 hairpin and initiation of HCR signal amplification. This is not disputed. Thus, in this case, the 1-4 overlap, even though it can be argued that the same or at least a similar technical function and result are therewith achieved, resulting in increased specificity, is not done merely as a work-around of the claimed inventions, but it has an accepted function of its own. In other words, the few nucleotides overlap is required for the different way in which the result is reached with the HCR Products according to the HCR protocol. This arguably leads to an improvement to the claimed inventions with the initiated amplification reaction to create a detectable signal in the context of the HCR protocol, which protocol was not envisaged in the patents in any way.

109. The Defendant therefore does not infringe the patents with its HCR products, neither literally nor by equivalence. It is not necessary to address whether the asserted allegedly infringing acts would have amounted to direct, indirect of joint infringement by Defendant.

III.E – CONCLUSION AND COSTS

110. As both patents are considered valid, the counterclaim for revocation is dismissed entirely. All requests in the infringement action are also dismissed because the patents are found not to be infringed.

111. Reasonable and proportionate legal costs and other expensed incurred by the successful party shall be borne by the unsuccessful party, up to a ceiling set in accordance with the RoP. The outcome in these proceedings means that the Claimant will have to pay the costs incurred by the Defendant in the infringement action, and the opposite is true for the counterclaim action, where the Defendant (claimant in the counterclaim) as the unsuccessful party, shall be ordered to bear the costs incurred by the Claimant (defendant in the counterclaim). The Court determines that the costs to be recovered cannot exceed the ceiling set for the combined case value in the claim and the counterclaim, i.e. EUR 800,000 in total. The Court sees no reason to deviate from this maximum in these proceedings. 50% of the ceiling amount is allotted to the claim and 50% to the counterclaim, thus EUR 400,000 to each. At the request of the Court, the parties submitted total cost estimates before the oral hearing, amounting to about EUR 716,000 for the Claimant and to (more than) EUR 800,000 for the Defendant.

112. Although parties did not reach a cost agreement before the oral hearing, the Court expresses the expectance that an agreement may be reached with these further clarifications. Remaining issues, if any, will need to be addressed in separate cost proceedings.

IV. DECISION

For all these reasons and after having heard the parties, the Court

in the main infringement action:

A. Dismisses the orders sought by the Claimant;

B. Orders the Claimant to pay to the Defendant reasonable and proportionate legal costs and expenses it incurred for the infringement proceedings, in accordance with Art. 69 UPCA;

In the counterclaim for revocation:

C. Dismisses the request to revoke the patents;

D. Orders the Defendant to pay to the Claimant reasonable and proportionate legal costs and expenses it incurred for the counterclaim proceedings, in accordance with Art. 69 UPCA.

Brinkman Presiding Judge	Edger Frank BRINKMAN Digitally signed by Edger Frank BRINKMAN Date: 2025.11.18 10:09:31 -03'00'
Zana Legally qualified judge	Alima ZANA Firmato digitalmente da Alima ZANA Data: 2025.11.18 11:27:18 +01'00'
Kokke Legally qualified judge and judge rapporteur	Margot Elsa KOKKE Digitally signed by Margot Elsa KOKKE Date: 2025.11.18 12:47:19 +01'00'
Alt Technically qualified judge	MICHAEL OLIVER Alt Digital unterschrieben von MICHAEL OLIVER Alt Datum: 2025.11.18 13:00:55 +01'00'
For the Deputy Registrar	Noua Mohammed Digitally signed by Noua Mohammed Date: 2025.11.18 12:44:26 +01'00'

Information about appeal

An appeal against the present decision may be lodged at the Court of Appeal, by any party which has been unsuccessful, in whole or in part, in its submissions, within two months of the date of its notification (Art. 73(1) UPCA, R. 220.1(a), 224.1(a) RoP).

Information about enforcement

(Art. 82 UPCA, Art. Art. 37(2) UPCS, R. 118.8, 158.2, 354, 355.4 RoP)

An authentic copy of the enforcement of the decision will be issued by the Deputy-Registrar upon request of the enforcing party, R. 69 RegR (Rules governing the Registry of the UPC).