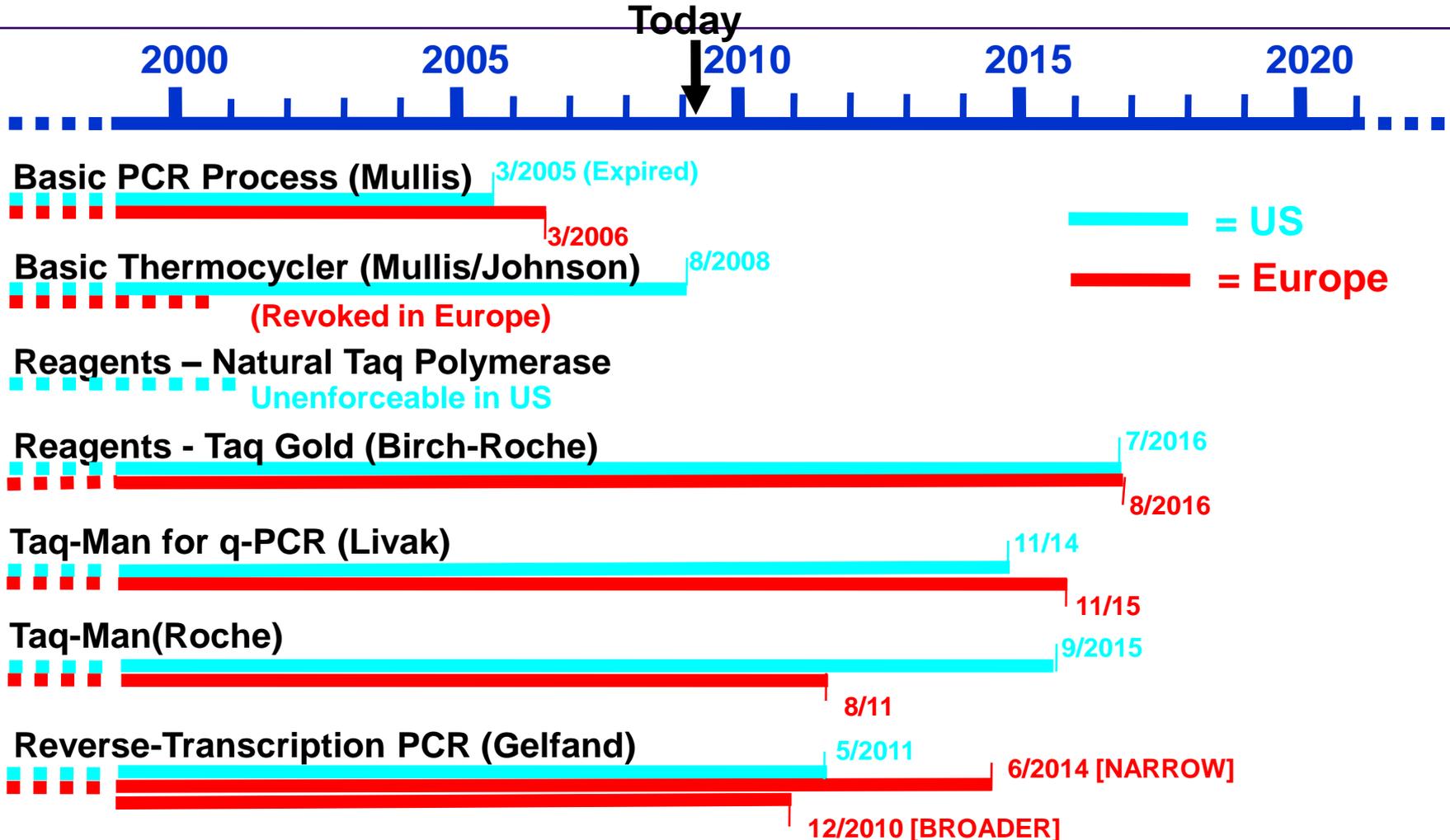


PCR IP Landscape

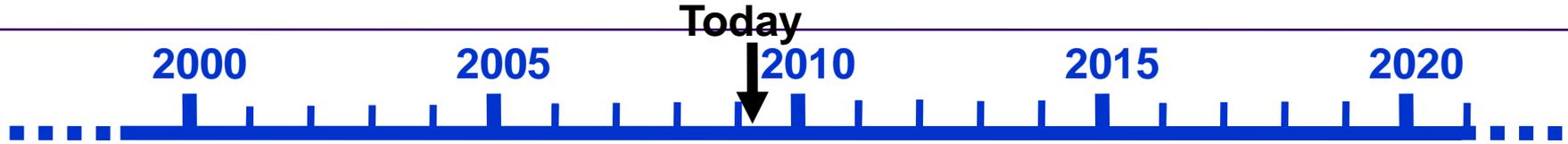
November 2009
VERN NORVIEL
QPCR Symposium

Not to be construed as legal advice

PCR Patent Landscape Summary- Some basics



Real-Time PCR



Real-Time PCR – Method (Higuchi-Roche)



Real-Time PCR – Apparatus (Higuchi-ABI)- US REEXAM- Currently rejected



Real-Time SYBR Green I – Method (Witter-Roche)



— = US
— = Europe

The First Wave of PCR Patents Have Expired

- The basic US PCR process patents have expired
 - Expired March, 2006 in Europe
- The basic US thermocycler patents (Mullis series) expired in 2008
 - Revoked in Europe
 - But note, there is one lingering Canadian patent
- Natural Taq polymerase patent held unenforceable in US
- **So, you can clearly perform basic PCR free of patents!
BUT.....**

Many Follow On Patents to Consider

- Improved Polymerases (2016+)
 - Roughly, they can be purchased/recommended, but may have DX limits
- Real Time PCR- Divided by Roche and ABI
 - *Method (2016)*- Roche- licensed reagents carry a “no DX” label license
 - *Device (2011/2012)*- ABI- US in reexam, EP just survived opposition, and JP is revoked
 - May only cover intercolating dyes
 - SYBER Green 1 in Real time – Roche (2016)
 - Reagents available, but no DX labels?

Follow On Patents (continued)

- Taqman-
 - Reagents available with license/ but with a no DX label?
- Reverse Transcription
- Miniaturized PCR
 - In EP only, miniaturized PCR claims issued broadly to Caliper
 - In US, Caliper & Affymetrix priority dispute recently resolved, but claims not issued
 - settlement terms not public

AND THERE IS A THICKET OUT THERE!!

- Owned by ABI (Applera)
- US patents expire in December 2012
 - Require a specific formula for calculating sample temperature and programming the computer to control the temperature. There are two US pending applications; one recites the formula and the other claims a particular sample tube design.
- EP 1157744 expires in November 2011

Claim 1. Thermocycler apparatus suitable for automated performance of the polymerase chain reaction comprising:

- (a) a metal sample block (12) having a major top surface and a major bottom surface,
- (b) an array of spaced-apart sample wells formed in said major top surface,
- (c) means (49) for applying bias cooling constantly to said sample block at a rate sufficient to cause said block, **if at a temperature within the range of 35-100° C**, to cool uniformly at a **rate of at least about 0.1 ° C/sec unless external heat is supplied**, and
- (d) computer-controllable heating means (156) responsive to said computer system capable of uniformly raising the temperature of said block at a rate greater than the bias cooling rate, said thermocycler apparatus being capable, under the control of a computer (20), of maintaining the array of sample wells at **a constant in the range of 35-100° C within a tolerance band of plus or minus about 0.5 ° C**.

MORE THICKET

- US 5,972,716 expires on April 29, 2014
 - relates to detecting fluorescence emitted from a sample tube (referenced Eppendorf tubes in the patent specification)

MORE THICKET- SAI

- US6800452
- Filed 8/8/1994, issued 10/5/2004
- Related to EP775298A2 (2, Withdrawn), US6746864 (3), US7427380 (3)
 - 1. A method for simultaneously performing a plurality of fluorescence assays using a multi-well plate containing a plurality of wells distributed throughout at least a portion of said multi-well plate, said method comprising the steps of:

distributing a predetermined amount of a liquid to a number of said plurality of wells;

projecting excitation radiation uniformly onto the portion of said multi-well plate throughout which the plurality of wells are distributed, thereby simultaneously and uniformly illuminating both said plurality of wells and the portion that is disposed between each of said plurality of wells;

receiving an image of fluorescence emitted from said plurality of wells simultaneously over a predetermined period of time; and

processing fluorescence data from the image.

University of Utah Research Foundation- Another thicket player

- US7238321
- Filed 7/13/2004, Earliest Non-Prov 6/4/1990
- Related to US5455175 (3), US5935522 (3), US6787338 (3), US7273749 (3)
- TD to 5,455,175 (Filed 1/10/1994, Issued 10/3/1995) (**Expires 2011**)
- No EP detected
- Independent claims
 - 1. A thermal cyler for amplifying a nucleic acid comprising:
a housing comprising a chamber;
a port in said housing for receiving at least one polymerase chain reaction (PCR) sample holder in said chamber;
a heating assembly for heating a sample comprising a nucleic acid contained in said sample holder, wherein said heating assembly is in thermal communication with said PCR sample holder when said sample holder is present in said chamber;
a cooling assembly for cooling said sample, wherein said cooling assembly is in thermal communication with said PCR sample holder when said PCR sample holder is present in said chamber; and
a controller programmed to control said heating and said cooling assemblies to cycle said sample holder and said sample through a predetermined temperature cycle corresponding to the denaturation, annealing and **elongation steps of a polymerase chain reaction within a time range of 30-60 seconds**;
wherein said PCR sample holder has a thermal mass which provides for completing said cycle of said polymerase chain reaction within said time range.
- Licensed to Idaho technologies

Stratagene- Another player in the thicket

- US2006289786
- Filed:05/02/2006
- Calculated to Expire:05/02/2026
- 1. An apparatus for sampling at least one sample of a biological material comprising:
 - at least one light source that emits an excitation light at defined intervals, wherein the excitation light interacts with the at least one sample; and
 - a detector sensitive to fluorescence emitted from the at least one sample; wherein the detector is continuously on.
- Status: Under final 103 rejection
- Family: No US children;
 - EP1880175A1
 - Claims have similar scope
 - Status: No action yet by the EPO; the ISR cited X and Y art over all the claims

Even in the thicket, there are many subtle points

THE REAL TIME METHOD PATENT

An instrument for use in monitoring a nucleic acid amplification reaction comprising multiple thermal cycles, comprising:

- (a) an automated thermal cycler capable of alternately heating and cooling, and adapted to receive, at least one reaction vessel containing an amplification reaction mixture comprising a target nucleic acid, reagents for nucleic acid amplification, and a detectable nucleic acid binding agent; and
- (b) a detector operable to detect a fluorescence optical signal while the amplification reaction is in progress and without opening the at least one reaction vessel, which fluorescence optical signal is related to the amount of amplified nucleic acid in the reaction vessel.

Higuchi Real-Time Thermocycler Patents

The Higuchi specification indicates:

“prior to the present invention, nucleic acid detection methods required a third oligonucleotide reagent as a probe.... The present invention eliminates the need for using a hybridizing probe reagent or a capture procedure for detecting the amplified target.” Col. 5, 48-57

[emphasis added]

SO.....

- Basic PCR is now an open field
- Many “tweak” patents exist
 - Some are available via licenses that have been issued for purchase of reagents
 - Of those, some are not available for diagnostics
 - Some have subtle points that require very detailed analysis
 - Many patents must be carefully reviewed to make sure a particular product is clear
 - A large number of the “tweak” patents expire in the next 2 years, and present minimal business risk
- In some cases, the situation in the US differs significantly from other countries